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BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Vol. XIII.—Nos. 131-132.] BALTIMORE, FEBRUARY-MARCH, 1902. [Price, 25 Cents.

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ON A SIMPLE METHOD OF PREPARING EPINEPHRIN AND ITS COMPOUNDS.

By John J. Abel, M. D.

(From the Pharmacological Laboratory of The Johns Hopkins University.)

Introductory.

I stated in my last paper[1] that my early empirical formula for epinephrin I had found to be too large by one benzoyl group $CO.C_6H_5$. This was in consequence of the singular tenacity with which this lone radical defied all but apparently destructive methods for its removal from the original benzoyl compound.

Elimination of this retained radical from my former series of compounds and substitution of the displaced hydrogen atom leads to the formula $C_{10}H_{11}NO_3$ as an adequate empirical expression for epinephrin as prepared by the methods hitherto employed by me.

It has also been shown in my previous papers that the substance which v. Fürth has called suprarenin is in reality nothing else than epinephrin. This suprarenin has thus far been presented only in the form of an impure iron compound for whose composition v. Fürth has not been able to deduce a rational formula.

His analyses show that the iron compound in question as prepared by him is of a variable composition. He, also by comparison with the commercial preparation, adrenalin, assumes that those fractions of his iron compound which show the highest percentage of carbon most nearly represent the true composition of the blood-pressure raising substance. These fractions give an average composition[2] shown by the expression $C_{8\cdot5}H_{12\cdot2}NO_x$, an expression that is only a rough approximation to the truth.

By making this iron compound in large amounts I was enabled to prepare from it an acetyl derivative, and, after saponifying it, to obtain enough material to prepare a picrate of epinephrin, from this a bisulphate and to convert

[1] This Bulletin, vol. xii, p. 337.

[2] Beiträge zur Chemischen Physiologie und Pathologie, Bd. i, S. 243.

this again into an acetyl derivative. This compound gave on analysis data that agreed well with those required for the triacetyl derivative of an oxy-epinephrin, $C_{10}H_{11}NO_4$.

The result of this analysis alone suffices to prove that suprarenin and epinephrin are one and the same body, except in so far as precipitation with ferric chloride and ammonia, or the conversion of the iron compound of suprarenin into its acetyl derivative without first removing its iron, has altered its composition.

In the paper already alluded to I have also maintained that adrenalin is only an impure modification of epinephrin, not fundamentally different. Both Aldrich and Takamine declare adrenalin to be the blood-pressure raising principle in the free state, "the base itself," as Takamine says. Aldrich[3] adopted the empirical formula, $C_9H_{13}NO_3$, as representing the elementary composition of his own adrenalin as well as that of the "purified" adrenalin of Takamine. Although this formula is a close approximation to that adopted by me for free epinephrin $C_{10}H_{11}NO_3$, it is, as I have shown, no more than an approximation to the truth, since it does not coincide with the analytic data of Aldrich. Furthermore, a study of these data has shown that no rational formula is deducible from them, that adrenalin, in short, as prepared and analyzed by Aldrich, is a mixture and not a chemical individual.

The same remarks will apply to the recent paper[4] by Takamine in which he describes his method of obtaining adrenalin. The average values of his elementary analysis are given in the following table[5] to which is added a calculation of the elementary values of his "probable empirical formula" for adrenalin, $C_{10}H_{15}NO_3$.

Found	Required for $C_{10}H_{15}NO_3$
C = 59.39	C = 60.91
H = 7.84	H = 7.61
N = 7.88	N = 7.11
O = 24.89	O = 24.37
100.00	100.00

Comparison of the required values with those actually found shows a deficit of 1.53% in carbon and an excess of 0.77% in nitrogen. No empirical formula can be made to fit these data, a sure proof of the fact that the substance analyzed by Takamine does not consist of a single, pure chemical individual. Crystalline it is, but not pure. Leaving out of consideration the analysis recently published by v. Fürth showing that a commercial specimen of adrenalin contained 57.84% of carbon and 8.11% of nitrogen, the analyses furnished by Aldrich and Takamine give nearly the same values for nitrogen, namely, 7.50% and 7.88%, while the values for carbon are 57.89% and 59.39% in the two cases, an inexplicable lack of agreement in the analyses of what is evidently one and the same substance.

Takamine, indeed, goes so far as to assert that his formula differs from that of Aldrich by CH_2.

More than three years ago I showed that the blood-pressure raising principle of the gland could be isolated in the form of active salts and that it was precipitated by ammonia, though in a physiologically inactive modification.

Takamine has precipitated this blood-pressure raising principle also by ammonia directly from a concentrated water and alcohol extract of the gland without previously forming chemical compounds of any sort and has found the resulting product to be crystalline and physiologically active.

Takamine dissolves the brown precipitate produced in the gland extract by ammonia in acidulated alcohol and removes inert substances as far as possible by the addition of ether. He then reprecipitates his substance out of this alcohol ether solution by means of ammonia. This is a method very unlikely to lead to a pure substance, for when a crude precipitate is obtained as above from an animal tissue and thus precipitated, it is highly probable that foreign substances are carried down with the compound which it is designed to throw out, and that in the subsequent washing with non-acidulated alcohol these will not be entirely removed. In support of this statement I need only mention that the commercial specimens of adrenalin that I have examined retain a sufficiently large amount of a phosphorus-containing substance to make their analysis impossible. One has only to fuse three or four grains of it with pure caustic potash and potassium nitrate in order to obtain with molybdic solution a very considerable precipitate of ammonium phosphomolybdate. In order to leave no doubt that we are here dealing with phosphorus I made control tests to prove the purity of my reagents and also transformed the phosphomolybdate referred to into the characteristic ammonia magnesium phosphate. I judge from the bulkiness of the phosphomolybdate precipitate that a quantitative experiment would result in a high percentage of an impurity.

On a Method of Obtaining Compounds of Epinephrin.

Convinced that the properties of epinephrin, as described by me, are inherent characteristics of the substance and that when they are not immediately apparent it is because some chemical modification has taken place, I sought new methods for the preparation of epinephrin in which the use of benzoyl chloride and the employment of the autoclave should be avoided.

Epinephrin as well as the modifications of it called adrenalin and suprarenin are all precipitated out of solution in acid alcohol with ammoniacal zinc chloride in the form of a flocculent white compound. v. Fürth was the first to make use of this salt as a precipitant of the substance that he obtained by decomposing a basic lead acetate precipitate from gland extracts with concentrated sulphuric acid, the precipitate being suspended in methyl alcohol.

[3] Amer. Journ. of Physiol., vol. v, p. 457.

[4] Amer. Journ. of Pharmacy, vol. 73, p. 523.

[5] I have corrected the arithmetical errors made by Takamine in calculating his averages.

In making an ammoniacal zinc chloride solution the basis of a method of isolation I determined to avoid the use of strong mineral acids and to employ hydrogen sulphide, both for the removal of zinc and for its reducing action and to end with ammonia as a precipitant exactly as in my first work.

The material that I started with consisted of the concentrated aqueous extract of 46 pounds of beeves' glands, or 3 gallons of a thick, turbid fluid, of grayish-white appearance. The filtrate is at first straw-colored but soon changes to a darker tinge on exposure to the air. This extract was prepared for me by Armour and Company of Chicago, and I take pleasure in again thanking this firm for their continued liberality in supplying my laboratory with expensive products of this kind.

This extract was prepared for me, like those formerly used, by repeatedly extracting the finely-divided glands at a moderate temperature with barely acidulated water, acetic acid being used in this instance. The extracts thus obtained were now brought to the boiling point for a moment to coagulate proteids as far as possible, then filtered and immediately concentrated under diminished pressure to the volume of 3 gallons. In extracting the gland I have made use of various acids, organic and inorganic, and have come to the conclusion that it makes no difference what acid is employed provided only that it is not an oxidizing acid and that it is used in *very great dilution*, as otherwise a peculiar converting action will be exerted by the mineral acids at least in the subsequent concentration. The change produced by strong mineral acids will be described at length in a later section of this paper.

In the original extraction it might also be well to steep the finely divided glands for a period of some hours in a vacuum apparatus at a temperature of 45° C., supplying water as fast as it distils off and keeping the whole mass in agitation the while, then filtering with a pressure apparatus until only a dry pulp remains.

The thick grayish fluid, above described, is filtered under pressure and thus a second time freed from a large amount of inert material. Three liters, for example, of this fluid were concentrated at a temperature of about 45° C. to a volume of 200 cc. This solution is poured into a tall cylinder, absolute ethyl alcohol[6] is added in small quantities at a time with constant and vigorous shaking until 1800 cc. of the absolute alcohol[7] have been added. At the conclusion of the operation the cylinder contains a large amount of a sticky precipitate which becomes granular in the course of time while the alcoholic solution has a light straw-colored tinge. After standing a few hours the alcohol is separated from the precipitate and distilled off under diminished pressure. A straw-colored syrup, which, on cooling, congeals to a clear golden-colored pitch, remains. This dissolves almost completely in an ammoniacal zinc solution. In repeating the experiment with the quantities described I have stopped the distillation when the volume of syrup reached about 60 cc. and while it would still flow freely. The solution in the zinc mixture is so complete that filtration is not necessary.

The ammoniacal zinc solution is now precipitated by the gradual addition, while stirring, of eleven volumes of absolute alcohol and set aside for some hours. During this period only a very slight increase in precipitation occurs. The precipitate, which for convenience may be labeled Zn I and which consists of a heavy, slightly reddish-yellow mass is removed, dried at 50° C. and powdered. It contains much epinephrin but a considerable amount remains also in the alcoholic filtrate, since the solubility of its zinc compound in strong alcohol is evidently increased by the presence of jecorin and other substances soluble in alcohol. This filtrate is now concentrated under reduced pressure, a little only of the fluid being poured into the flask to start with and the rest supplied continuously as the distillation proceeds, the object of this being to carry off water as far as possible in company with the alcohol. When this alcoholic solution has been reduced to a volume of 50 or 60 cc. absolute alcohol is added until its volume reaches 100 cc.; three volumes of ether are now added in small portions at a time, with vigorous agitation, and immediately a sticky, ropy precipitate is found adhering to the bottom and sides of the vessel. This precipitate we will designate as Zn II. The very little epinephrin remaining in the alcohol-ether mixture is deposited in the course of time.

PROPERTIES AND FURTHER TREATMENT OF THE ZINC PRECIPITATES.

We now have the epinephrin of the gland in the form of a zinc compound in two precipitates, Zn I and Zn II. The former, when dried and powdered, has the appearance of slightly discolored flour; the latter might perhaps also be dried and powdered, but no attempt was made to alter its appearance. Zn II is small in bulk as compared with Zn I and dissolves with the greatest ease in very dilute acetic acid while Zn I requires repeated treatment with the same for its solution. It of course contains much besides the zinc compound of epinephrin, as is probably also the case with Zn II, but nevertheless it can be almost completely dissolved by the above method.

The combined fluids required to dissolve Zn I and Zn II amounted to 250 cc. and contained only enough acetic acid to effect the solution.

The zinc was now removed with sulphuretted hydrogen, and the resulting zinc sulphide washed until the filtrates gave only a slight reaction for epinephrin with ferric chloride. The original filtrate and the washings were reduced under diminished pressure to about 30 cc. when a fluid of a somewhat reddish color, but entirely transparent, was obtained.

[6] In some of my earlier work, I made frequent use of methyl alcohol as a precipitant and found that it answered the purpose equally well.

[7] I have also used zinc chloride in alcohol at this stage to precipitate foreign substances, but have not yet carried this solution through to the end.

Behavior toward Excess of Ammonia.

When to a beaker containing the above fluid ammonia[1] of specific gravity 0.944 is added until the reaction is plainly alkaline, no change is produced, except that the clear solution becomes slightly redder. If now this strong ammonia is added boldly in such a manner that it flows down the sides of the beaker, a striking change soon takes place.

At the line of demarkation between the two liquids a white turbid zone appears which soon resolves itself into a mass of crystals which fairly rain to the bottom of the beaker. On being stirred with a glass rod, the fluid becomes a mass of crystals and the odor of ammonia which before was intolerably strong, entirely disappears. The solution is still strongly alkaline, but the reaction has only begun; fresh portions of ammonia are added only to be absorbed in turn as each new crop of crystals falls to the bottom or adheres to the sides of the flask. The reaction is not complete until the striking avidity of the solution for ammonia is entirely satisfied, in short until the solution smells strongly and permanently of ammonia. At this time the fluid above the crystals is of a light straw color, but in a short time it takes on a pink tinge due to the oxidation of the epinephrin that still remains in solution, and this color deepens during filtration, which should immediately follow the operation just described. If filtration be delayed for a day, the supernatant fluid becomes black and a not inconsiderable loss occurs from resolution and oxidation of the precipitate. Once prepared the compound may be repeatedly crystallized out of its solution in hydrochloric acid by the free addition of ammonia with slow stirring.

On the Effect of Gradual Additions of Ammonia at Intervals of Time.

In my first trial I made the solution plainly alkaline with ammonium carbonate, added what I feared was an excess of ammonia and set aside overnight. The next morning only a thin layer of crystalline nodules was found at the bottom of the beaker with a very dark-colored fluid above. These crystals were removed and washed with water and more ammonia was added to the now somewhat diluted filtrate. On stirring with a rod and again setting aside, an abundant crystalline precipitate fell out of the dark fluid. On repeating the filtration and again adding ammonia, the same result followed. This avidity for ammonia observed in solutions prepared as above, although they were all the while strongly alkaline, led me to the bolder use of ammonia.

In a later paper I shall discuss at more length the chemical reactions that are involved in this liberal use of ammonia and shall attempt to show why epinephrin is here precipitated in the form of a crystalline substance. v. Fürth has maintained that the substance with which I have been so long working cannot be the blood-pressure raising principle of the gland for the reason, among others that have also been refuted, that in its native state as found in an aqueous extract of the gland, it is not precipitable by ammonia. I was able to show in reply to this criticism that every compound of epinephrin is precipitated in its flocculent, inactive state by ammonia if it has first been subjected to hydrolytic treatment, while at the same time I admitted the truth of his statement that the native product is not precipitated by ammonia and this, it is now seen is true only for the dilutions with which he and I were then working.

A year ago I subjected the suprarenal glands to the action of the papoid ferment, made extracts of the digested mass by the use of water and a series of organic fluids and treated the resulting products with ammonia and ammonium carbonate, always making plainly alkaline and setting aside. The result was always unsatisfactory, only a very minute amount of substance mixed with oxidized epinephrin and foreign material being obtained. My later experiments showed me that an abundance of ammonia is required and that the active principle must be present in the solution in large amounts.

The substance as thrown out by ammonia is strongly basic, it also reduces Fehling's solution with precipitation of cuprous oxide. The cause of this changed behavior toward Fehling's solution after exposure to the action of ammonia will also be discussed in a subsequent paper.

In its behavior toward Fehling's solution, ferric chloride silver nitrate and a few other reagents, it agrees with my former preparations, but unlike these it fails entirely to give the alkaloidal reactions that characterize epinephrin. I shall soon publish analyses that will show to what extent this crystalline substance agrees in composition with the similar and probably identical compound contained in the material analyzed by Aldrich and Takamine.

Conversion of the Substance Isolated by the Zinc Process into Epinephrin.

Whatever differences in elementary composition may be found to exist between this substance and epinephrin, $C_{10}H_{11}NO_3$, it is certain that the former may easily be converted into a physiologically active substance that gives all the characteristic reactions of epinephrin. The following experiment will illustrate this conversion:

Epinephrin Hydrochloride.—One gram of the crystalline compound, after being twice recrystallized and freed as far as possible of the alkaline gas which is constantly being evolved from it, was dissolved in 1 cc. of hydrochloric acid of specific gravity 1.19 and absolute alcohol was added to the volume of perhaps 20 cc., the solution continuing to be perfectly clear, though of a slightly reddish tinge. 80 cc. of ether was now added in small portions at a time until no further precipitation of epinephrin hydrochloride occurred. The precipitate was now dissolved in a small volume of absolute alcohol and again precipitated by ether. As thus prepared, this salt falls out in the form of white masses and separate particles which

[1] I employed ammonia free of pyridene which, however, is not at all necessary for the success of the experiment.

cling to the bottom and sides of the vessel. It is transferred rapidly to a filter, washed with a mixture of alcohol and ether in which it will not dissolve and then immediately transferred to a desiccator and dried in vacuo.

Epinephrin Sulphate or Bisulphate.—This salt is made in the same way, being first dissolved in as little strong sulphuric acid as possible of about 90%.

It is likely that much weaker sulphuric acid than the above will effect the transformation into epinephrin, my object in using acid of this strength was to avoid an excess of water in order that the epinephrin sulphate might not be precipitated in a gummy state.

Both salts are extremely hygroscopic, so long as traces of ether still cling to them. When precipitated in alcohol by ether with the greatest possible exclusion of water, their appearance, when examined with a pocket lens through the flask is suggestive of the micro-crystalline state. Whether these salts are really crystalline can only be determined by precipitating in the field of the microscope. Once exposed to the air, while still moist with alcohol or ether, they lose their crystalline character, if indeed they ever possessed it.

After being thoroughly dried, both salts may be reduced to a white powder. Both salts have now lost their hygroscopic quality, both are very soluble in water and behave like acids toward litmus, a behavior which cannot be due to adherent acid used in their preparation. Experiments in the way of crystallizing these salts are now being made.

From the concentrated aqueous solution of these salts a picrate may easily be formed, and from this I expect to derive salts of other organic acids.

As tested in dilute solution these salts are found to have a powerful constricting action on the blood-vessels of the conjunctival sac. As one affinity is not neutralized by a retained benzoyl group, I entertain the hope that they will surpass the members of my former series in physiological activity and even that of the sulphate of doubtful purity derived from a basic lead acetate which was tested by Professor Reid Hunt.[1] The therapeutic importance of such very soluble and stable salts of epinephrin is apparent.

Behavior of these Salts of Epinephrin toward Alkaloidal Reagents.

Mandelin's reagent applied to the dry substance gives the characteristic and delicate play of colors from a yellowish-red to an olive-green formerly described in the case of the mono-benzoyl series.

Stirring a crystal of potassium permanganate into a solution of the dry substance in concentrated sulphuric acid gives rise to a rich plum color. Adrenalin also gives this reaction.

Picric and tannic acids, solution of iodine in potassium iodide, iodine trichloride, phosphotungstic acid (one part to 20 of water with a little hydrochloric acid), and phosphomolybdic acid, all give precipitates, some of them in solutions of the greatest dilution. Stronger solutions are also precipitated by gold chloride, platinum chloride and by zinc chloride in 50% solution.

This list can no doubt be greatly extended, but for the present it will suffice to illustrate the remarkable action of strong acids in thus altering the character of the original substance.

These salts of epinephrin also differ in another noticeable way from the substance made by the zinc process. On the addition of lime water to equal quantities of each, the odor of the coniine-piperidine-like base, to which I have so often referred rises very quickly from the latter, but only after a considerable time, from the former.

Action of Ammonia on the Salts of Epinephrin.—Equally striking is the changed behavior of this epinephrin toward ammonia. The addition of this reagent to an aqueous solution of these salts results not in a crystalline precipitate of strongly basic character but in the immediate production of a yellowish-white flocculent precipitate which easily re-dissolves on the addition of strong ammonia. This solution rapidly darkens and if it is sufficiently concentrated in the first place, a reprecipitation in the form of nodules or granules occurs. I take it that this reprecipitate is an oxidation product of the original flocculent precipitate.

If the flocculent precipitate is rapidly transferred to a filter and washed with cold water, alcohol and ether it may be obtained in the form of a gray powder. This has not yet been tested as to physiological activity, but it agrees in all its other characteristics with the corresponding mono-benzoyl epinephrin of my former papers. It still retains its power to reduce copper sulphate and shows all the other reactions of epinephrin.

We are ignorant of the state in which the blood-pressure raising principle exists in the gland. We have seen that under the influence of strong ammonia it falls out of an extract of the gland as a crystalline compound of markedly basic properties and that exposed to the action of acids it is changed to an apparently very different substance of feebly basic or acid properties.

We have also seen that the former variety may easily be changed to the latter by exposure to the action of acids. The reconversion has not yet been effected, but I hope to accomplish this also, or at least to throw light on the chemical process involved in the first conversion.

Note on the Character of the "Autoclave Effect."—The described action of sulphuric and hydrochloric acids on the modification of epinephrin isolated by me by the zinc process throws light on what I have hitherto called the autoclave effect. In my early work on this subject I made use of this apparatus in the saponification of my benzoyl derivative with dilute acid and I did so to avoid oxidation as far as possible. In consequence of the temperature used, the dilute acid that was used as a hydrolyzing agent acted as do strong acids at room temperature in the experiments above described.

[1] Am. Journ. of Physiol., March, 1901.

On the Decomposability of the Crystalline Derivative of Epinephrin as prepared by the Zinc Process and by other still Simpler Methods.

An alkaline gas is continually being evolved from the crystalline derivative at room temperature, as the following experiments will prove:

Exp. I. A small portion of the compound as made by the zinc process was twice crystallized out of its solution in dilute hydrochloric acid by the free addition of ammonia, a small amount being taken to insure perfect washing. After the last crystallization, the material weighed about one gram.

It was washed with water until no trace of chlorine could be detected by silver nitrate and nitric acid, either in the filtrate or in the substance itself. The products of the energetic oxidation that results on boiling with these two reagents will be the subject of a later paper. The substance was next washed with absolute alcohol, then with ether and exposed at room temperature until dry. It was now spread out on a watch glass and a second watch glass placed over it, to whose inner surface a strip of moist red litmus paper was attached. In the course of two hours the free edges of the strip had turned blue.

Exp. II. A larger portion of the substance, about 6 grams of finely crystallized material was recrystallized and washed in the manner just described until the absence of chlorides was assured, the washing being continued for some time even after it might safely have been assumed that no free ammonia was present.

As fresh amounts of water were added, the material was frequently stirred with a glass rod, and the freely-dripping filtrate was each time drawn off by gentle suction. A brief washing with absolute alcohol then followed and the substance was spread out on the bottom of a crystallizing dish which was placed under a similar vessel containing 10 cc. of sulphuric acid of such strength that 50 cc. contained three drops of 25% sulphuric acid and gave a bright red color to a litmus solution. Over this a bell jar was placed. In a short time a change in the tint of the litmus solution was observed and twenty-four hours later it had assumed a distinctly blue color. When this dilute sulphuric acid was replaced by a fresh portion, it also was made alkaline in the course of twenty-four hours. After standing a week it seemed to yield about as much of the alkaline vapor as at first. On boiling with water a portion of the substance that had been thus exposed over dilute sulphuric acid I observed a further liberation of ammonia.

Exp. III. The adrenalin of commerce gives off even more of this alkaline gas than does the preparation above described. One has only to make the watch-glass test with 60 mg. of this substance in the dry state to find the strip of moistened red litmus paper used turn entirely blue in a short time.

It is evident that we are here dealing with a very decomposable substance, not a stable one as Aldrich and Takamine have stated it to be. Add to this fact that commercial adrenalin is rich in phosphorus and that the published methods of preparing it do not guarantee the absence of phosphorus-containing compounds and we have a full explanation of the illy concordant analytical results which these observers have obtained.

I assumed in my last paper that the so-called adrenalin is in reality impure epinephrin, $C_{10}H_{11}NO_3$, in the free reduced state, and I offered several suggestions to explain why Aldrich's analyses did not square with the above formula, calling especial attention to the high nitrogen content of his substance. It now appears that both Aldrich and Takamine have tried to analyze a substance which is constantly giving off nitrogen in the form of an alkaline gas. Aldrich, indeed, dried his substance over sulphuric acid in vacuo.

On the Nature of the Alkaline Gas emitted by the Compound.

In the absence of analyses it is not as simple a matter as might be supposed to identify the alkaline gas referred to, or, what is more important, to state in what form it leaves the gland. I placed a filter containing about 10 grams of freshly-prepared but moist material made by the zinc process and thoroughly washed into a desiccator charged only with calcium hydrate, and 12 hours after, it was found to be filled with an alkaline gas which had an odor like that of ammonia. But if to the dilute sulphuric acid used in Experiment II sodium hydroxide be added, an odor is obtained like that of methyl amine, that is, both ammoniacal and fishy. And yet if, to even large amounts of the substance which has been long exposed to air, sufficient sodium hydrate be added to dissolve it, neither the ammoniacal nor the fishy odor arises. At room temperature no odor whatever is given off by this alkaline solution for the first few moments, but if it is gently warmed, the characteristic and offensive odor of the substance that I have called the coniine-piperidine-like base becomes evident. This simple experiment suffices to prove that we are not dealing here with a simple but easily dissociable ammonium salt of epinephrin, not at least *after* the substance has been exposed to moist air for a long time.

Later I observed that if the dilute sulphuric acid be removed entirely from the bell jar in Experiment II, the substance itself will give off this same coniine-piperidine odor. It is impossible to dry our substance in a drying chamber even at a low temperature, at least in the presence of air without losing much of this odoriferous constituent, as the drying oven soon becomes filled with its fumes. It has also been shown in this paper that this crystalline derivative of epinephrin emits this volatile gas much more easily on the addition of lime water than does the epinephrin into which it is converted by mineral acids when treated in the same way.

I have shown in an earlier paper[10] that this volatile base

[10] Zeitschr. f. physiol. chem., Bd. xxviii, S. 344.

undergoes decomposition when we attempt to distil it from an alkaline aqueous solution. From all that has been said above it would appear probable that the alkaline gas which is spontaneously liberated from the crystalline base owes its origin to that part of the molecule which I have called the coniine-piperidine-like substance and that this substance undergoes further decomposition into a primary amine or some other ammonia base, according to the circumstances of the case. This is not meant, however, to exclude the possibility of the formation of a dissociable ammonium salt in the first instance.

On Simpler Methods of Preparing the Compound under Consideration.

Both Aldrich and Takamine state that other alkalis may be used in place of ammonia in precipitating their adrenalin, but that ammonia is to be preferred because of the solubility of adrenalin in fixed alkalis. On making free use of ammonia, I found that a very fair yield of the substance could indeed be obtained from a concentrated aqueous extract of the gland without the use of zinc hydrate, ferric chloride, lead acetate, precipitation with ether or other methods of purification. These measures are entirely unnecessary as far as the mere precipitation of the substance is concerned, although, of course, so pure a substance is not obtained as when the zinc process is used.

Only two operations need precede the use of ammonia or other alkali: evaporation of an aqueous extract of the gland, the preparation from this of an alcoholic extract and the removal of its alcohol. After this last step the free use of ammonia results in the formation of the same crystalline compound described above with the same accompaniment of ammonia absorption by the alkaline solution. Experiments made more than a year ago lead me to suspect that absolute alcohol saturated with ammonia or containing the fixed alkalis will not precipitate our substance out of its solution in strong alcohol, or at least only imperfectly; in other words, that the presence of water is necessary to the success of the reaction.

On the Substitution of other Alkalies for Ammonia as a Precipitate.

Exp. I. On adding to the water-alcohol extract just described a 25% solution of potassium hydrate, no change was at first produced, the solution did not change color nor did it give off the odor of ammonia nor of a primary amine. In a few moments, however, a precipitate began to fall out. After prolonged washing with water and alcohol it was obtained as a snow-white powder, which, when examined under the microscope with a low power, appeared to be amorphous. In its chemical behavior it seemed to be identical with the substance obtained by the zinc process. Like that it also evolved an alkaline gas.

Exp. II. Thinking that it might possibly be contaminated with some other constituent of the gland which had united with the alkali and formed an insoluble compound with it, I made the following experiment:

Two grams of the twice crystallized compound made by the zinc process, a compound which certainly appears to be a definite, although highly unstable chemical individual, was dissolved in a requisite and known amount of dilute sulphuric acid. This was at first neutralized by the addition of 1/10 N potassium hydrate, but seeing that the solution would become too dilute for the purposes I had in view, I added a 25% solution of the hydrate, drop by drop, until the precipitate that had fallen out in consequence of the neutralization of the sulphuric acid employed, had entirely redissolved.

Of course a considerable excess of potassium hydrate was now present in the solution and this had assumed a dark brown color. Ammonia in excess was now added, and in the course of an hour or two about half of the original material had crystallized out in the form of small prisms clearly visible with a pocket lens.

Exp. III. Calcium oxide was added in small quantities to some of the material used in Exp. I. As soon as the fluid was saturated with this alkali, it became turbid and a little of the compound under discussion fell out. Further experiments showed that the crystalline base made by the zinc process is to a very large extent soluble in lime water at room temperature. Only material that had long been exposed to air was used, and such material always leaves a residue which does not dissolve in further amounts of lime water. On the addition of ammonia to such a solution in lime water no precipitate is produced, but if much alcohol and then ether is now added, a dark flocculent precipitate of amorphous epinephrin soon falls out. Further experiments will throw light on this peculiar action of ammonia in the presence of calcium hydrate and will show the relation that exists between this experiment and those described in connection with the action of mineral acids.

I will add that in Experiment I, ammonia was added to the filtrate after the removal of the potassium-containing precipitate and a further amount of the substance equal in bulk to that previously thrown out by the fixed alkali was obtained. The above experiments suggest the possibility of forming a series of alkali derivatives.

I have described a sufficient number of experiments in proof of the fact that the crystalline derivative of epinephrin prepared by the zinc process and by other still simpler methods is a highly unstable substance, that it evolves an alkaline gas at room temperature, that it can be converted by the help of mineral acids into epinephrin itself, although possibly into a form richer in nitrogen than that of my former series. It might seem to be in order to give a more definite expression of opinion as to the true rôle played by ammonia and other alkalis in the experiments described and also as to the relationship that exists between epinephrin and the crystalline compound from which it is derived. Similar relationships are well known to chemistry and a number of possibilities present themselves by way of explanation. I

prefer, however, to await the outcome of my analytical work before committing myself to anything further than a statement of facts.

SUMMARY.

1st. The blood-pressure raising constituent of the suprarenal gland may be isolated by the method described in this paper in the form of a basic, minutely crystalline though unstable compound which agrees in some of its properties with the substance that I have called epinephrin, while it fails to exhibit certain other equally fundamental and characteristic properties of this substance.

2d. Mineral acids, however, easily convert this substance into one which is physiologically active and which also gives all the characteristic reactions of the epinephrin, $C_{10}H_{11}NO_3$, contained in my former series of compounds. Highly soluble and apparently stable salts of therapeutic and chemical importance are therefore easily made.

3d. Analyses of the substances described will soon be given to show what changes, if any, in elementary composition take place under the influence of the acids used in the conversion; also how these new compounds of epinephrin will agree in composition with those of my former series; also, how far the substance isolated by the zinc process agrees in composition with the similar and probably identical compound contained in the material analyzed by Aldrich and Takamine.

A NEW COMBINED ELECTRO-CAUTERY INCISOR FOR THE BOTTINI OPERATION FOR PROSTATIC OBSTRUCTION.

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Although the electro-cautery operation was brought out by Bottini as far back as 1876, it was not generally adopted until 1897, when Freudenberg presented to the profession a greatly improved instrument, and followed it up by numerous convincing articles. During the past four years this operation has been performed very extensively, and we are now in a position to stop a moment, look over our results, and discuss the shortcomings of the operation, as well as its merits.

Freudenberg's large collection of operated cases probably shows very accurately the value of the procedure. The statistics are as follows: 752 cases, in which the result was good in 86½%, a failure in 7½%, and the mortality between 4 and 6%.

These figures, if correct, undoubtedly show much better results than can be claimed for any other operative procedure. Castration, while peculiarly effective in a certain class of cases, has been wofully unsatisfactory as a routine procedure, and has justly been relegated to the list of operations historically interesting, but practically valueless.

Prostatectomy thoroughly performed is undoubtedly an operation of great value. There is no question that the statistics as to the value of this operation are entirely misleading, for many reasons; principally because in most of the recorded cases (and in all until recently) the operation was entirely inadequate—merely a nipping off of the most evident intravesical projections, leaving the equally important parts of compression in the deep urethra untouched. There is no question, however, that a thorough removal of the entire gland, which can generally be easily accomplished by enucleation with the finger, is a very successful operation, and entirely satisfactory when perfectly accomplished.

There are, however, several varieties of prostate which are unsuitable for this operation, principally the small and the sclerotic varieties. This, however, is not the principal objection, but the fact that in the majority of instances we are confronted with patients too old and too feeble to safely undergo the shock of a satisfactory prostatectomy. It is for just this class of cases that the Bottini operation has proved such a blessing, and has achieved really wonderful results. On account of the success of the cautery operations in the otherwise hopeless cases, it has become more and more the question whether it should not become the method of choice in all manner of cases. Since there are, however, a certain number of failures (10% or more) and a certain mortality (between 5 and 8%) shown by the Bottini operation, it still remains questionable whether it should replace prostatectomy, especially in younger patients. To settle this point more extended investigation is necessary. It also behooves us to study the causes of failure and fatality in the Bottini operation, with a view of finding means of obviating both as far as possible.

Among the causes of death besides uremia, shock, sepsis, etc. (presumably unavoidable), we find recorded several not unavoidable reasons, principally from improperly placed or too lengthy incisions. In the first category are deaths from the cautery blade burning its way into the rectum, due, as has been shown by Freudenberg, to the fact that the beak of the instrument became caught in a post-ureteral pouch, which is separated by only a short space from the rectum. In the same class are those fatal cases in which the entirely useless anterior cut was made and penetrated (as might have been expected) into the space of Retzius. In the second category are a number of cases in which the operator has

rashly made his incisions too long, resulting in the rupture of the urethra in front of the prostate, and sometimes fatal hemorrhage from division of perineal vessels.

The statement of certain writers that incisions of 4½, 5 or 6 cm. in length were often necessary to remove the obstruction is absolutely without pathological substantiation, and undoubtedly liable to lead to a great many serious blunders in the profession. Very rarely, even in the very largest hypertrophies, should an incision over 3½ or 4 cm. be made, first because it is unnecessary, and secondly because it is dangerous. Deaths from any of the causes outlined above are preventable, and should in the future be eliminated from the statistics.

In Freudenberg's statistics, after excluding the fatal cases (4.2%), we find 92% improved, 55% cured, 37% definitely improved, and 8% failures. Why should there not be a greater uniformity of results? Is the operative technique, or the instrument at fault? Turning to the instrument, we find the one of Freudenberg much preferable to that of Bottini, as has been very frequently pointed out. But there are several very evident weaknesses in even the former instrument. In the first place, since there is the greatest difference as to size, shape and condition among hypertrophied prostates, it is unreasonable to expect one single cautery blade to be suitable for all. An incision which is plenty deep for a medium-sized hypertrophy may be wholly inadequate for a very large one, and positively dangerous for the small fibroid forms. Then, again, one lobe is often very greatly enlarged while another is only slightly so. Are we, then, to give each the same depth of cautery incision? I have in my collection of autopsy specimens several prostates with small but very obstructive middle lobe enlargements, where the ordinary Freudenberg and Bottini instruments would have penetrated beyond the capsule and perhaps into the rectum.

It is very evident, then, that an instrument with several easily interchangeable blades of graded sizes would be a decided improvement.

There are two other defects in Freudenberg's apparatus which, while apparently trivial, are of considerable importance. The first is in the shape of the beak of the instrument as now constructed. The traction necessary to hold the beak up against the prostate during an operation will often pull it into the urethra. This is due to the fact that the beak meets the shaft at such a wide angle (or at such a slope) [see Fig. 7] that even moderate traction causes it to ride over a median bar (for example) and slip into the prostatic urethra. The dangers of this accident are not small. Indeed it has occurred several times, and has been responsible for several deaths, the cause being division of the membranous urethra, extravasation, hemorrhage, etc. In order to be certain that the beak of the instrument is against the prostate, and has not slipped into the urethra, Freudenberg has wisely advised that a finger be inserted into the rectum to determine its location before an incision is begun.

I have carefully followed this practice for the past two years, and have thus prevented several accidents, for in numerous instances have I found that a little steady traction (as in an operation) would draw the beak into the urethra. But this safeguard is not always sufficiently accurate, for while it is comparatively easy to feel the tip of the instrument turned downward toward the trigone, one cannot often feel the beak with sufficient certainty when the instrument is turned to make a lateral cut, as one of my own cases demonstrated to my sorrow (Freudenberg's instrument was being used). The forefinger of the right hand was inserted into the rectum, and the tip of the beak definitely located to be in the bladder. The rotation was made for a lateral cut, and with the finger still in the rectum traction put upon the instrument to draw the beak up snugly against the prostate. The beak was not felt to slip into the urethra, but before beginning the cautery incision another careful examination with the finger (which was kept in the rectum during the entire operation) was made and did not reveal any slipping of the beak. Despite all these precautions (which happened to be unusually carefully taken in this case) an incision of 3½ cm. was followed by a gush of blood from the meatus, and a perineal section done under cocaine revealed a ruptured membranous urethra, and extravasated blood behind the triangular ligament. A timely operation saved his life, but it brought very forcibly to my mind the *need of a beak which would not slip into the urethra*, one more nearly at right angles to the shaft.

The other defect, at times quite disagreeable, was that the handle of the instrument would often become so greatly heated as to burn the hand of the operator, and sometimes to prevent his turning the contact screw to break the electrical current. Examination soon showed that this was due to bad contact. This connection was made by a flat surface coming against a cylinder, resulting in a linear contact, insufficient to conduct the high current necessary to heat the instrument without itself getting hot. This defect, while merely one of mechanical construction and easily remediable by bringing broader areas into contact, was one which frequently led to great trouble both on account of the heating of the handle and the insufficiency of the electrical current which reached the cautery knife.

Recognizing more and more during two years' work with Freudenberg's instrument the drawbacks referred to, and especially, feeling the need of blades of different size, the writer finally consulted the Kny-Scheerer Co. of New York,[1] during April, 1901, with reference to the construction of an instrument which would, if possible, fill all the requirements. After considerable experimentation we have produced, we believe, a satisfactory instrument, the construction of which is thoroughly explained by the accompanying cuts.

As seen in the illustrations, the form of Freudenberg's

[1] My thanks are due to Mr. Charles Farner, mechanician, for valuable help.

instrument is adhered to (Fig. 1), the only changes being in its having four interchangeable blades, a beak of different angle, a connecting handle with more extensive contact surfaces, and a few minor changes in construction. By a very simple device, the simple elevation of a sliding bar on the rotary wheel, one blade may be removed and another inserted

Blade No. 3 corresponds to the one usually found in Freudenberg's instrument, and is the one most generally used, while No. 2 is useful in small hypertrophies, and No. 4 for the very large. Blade No. 1 (the smallest) was constructed mainly to complete the set, and without any idea of much practical value. I have been surprised, however, to

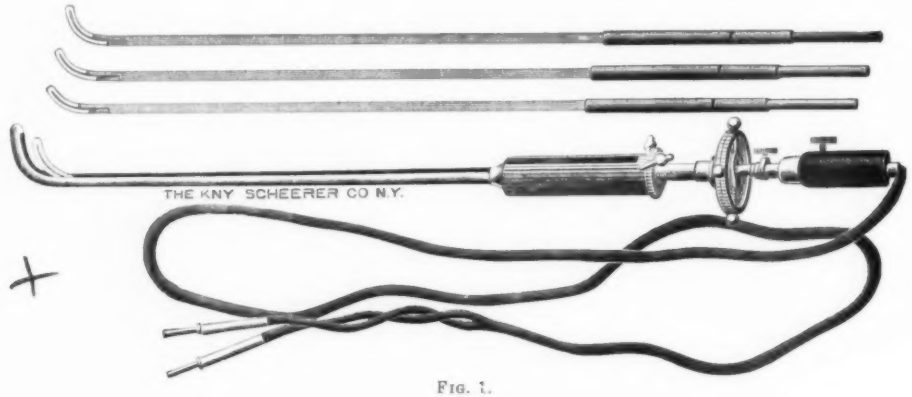


Fig. 1.

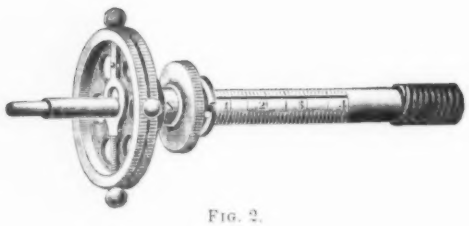


Fig. 2.

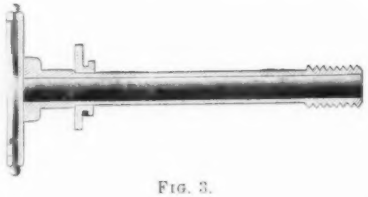


Fig. 3.

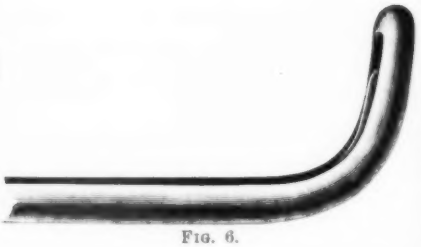


Fig. 6.

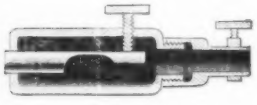


Fig. 7a.

Fig. 4.

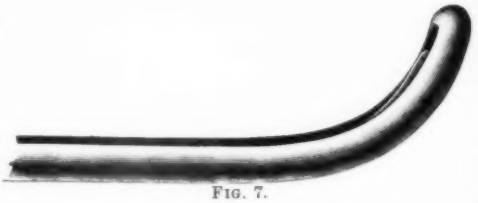


Fig. 7.

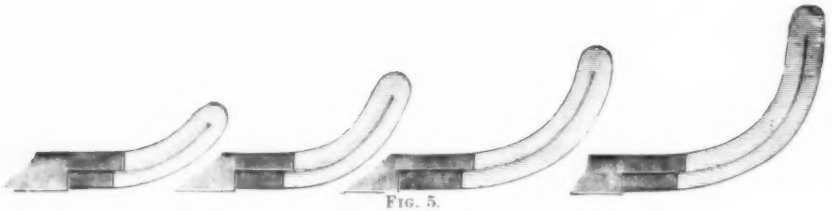


Fig. 5.

(Figs. 2 and 3). The sliding bar working on a spring holds the rod containing a blade firmly attached to the screw mechanism by engaging the circular groove near its outer end (Fig. 4). We have had four blades constructed as shown in Fig. 5. The smallest having an elevation of .8 cm., the second 1.2 cm., the third 1.7 cm., and the fourth 2.1 cm.

find it very useful in several cases, which will be given in detail further on.

The change in the shape of the beak has been of very great comfort. The new beak (Fig. 6) cannot possibly slip by the prostatic orifice into the urethra with all the outward traction which may be put upon the instrument during

the operation, whereas with the Freudenberg instrument (Fig. 7) one must be constantly on his guard lest this occur. The right-angled character of the beak does not make it any harder to introduce, in fact it seems to ride over a high median bar with greater ease, having more the shape of a prostatic catheter.

The changes made in the instrument handle of the conducting cable, as shown in the diagrams, consist merely in bringing larger surfaces into closer and firmer contact. To accomplish this we have placed beneath the end of the contact-making thumb screw a metal spring, having on its end a concave contact block (see Fig. 7a) made to fit the circumference of the end of the male blade. Another thumb screw has been placed at the end of the handle to insure tighter contact at the other connection. These changes have completely done away with the disagreeable over-heating of the contact screw, which constantly occurred before, and which was undoubtedly due to insufficient contact, as described above.

During the past five months I have used this instrument on sixteen cases, and have amply proved it to be practical, and one, I think, that has overcome many of the defects to be found in Freudenberg's instrument.

We will give in abstract a few illustrative cases, but before doing so it may be well to state the measures we take to determine before operation the size, shape and character of the prostatic enlargement, and consequent selection of the blade to be used, and the length of the cuts.

Besides a systematic general physical examination, noting particularly the condition of the arteries, a very careful local examination is made as follows: *Rectal examination*, noting: the size, shape and consistence of the prostate; the relative enlargement of the two lobes, the thickness of the prostate as revealed by the finger in the rectum, and a sound in the urethra (determining in this way the thickness of the hypertrophy in the median portion); the adnexa of the prostate, vesicles, glands, rectal mucosa, etc. *Bladder examination:* 1. with catheter, noting the location, depth and character of prostatic obstruction, with residual urine, the capacity of the bladder and its tonicity. 2. With the cystoscope, noting: (a) the size, shape, location and character of intravesical prostatic hypertrophy (especially as to the condition of the median portion, whether a bar or a rounded or pedunculated lobe, and its elevation above the trigone (bas fond); the relative enlargement of the lateral lobes, etc. (b) The condition of the bladder wall; as to trabeculation, pouch formation, diverticula, inflammation, ulcers, calculi, etc. 3. With searchers (in absence of a cystoscope), which by rotary movements may determine quite accurately the presence of a middle lobe; and the relative size of the lateral lobes, as also the presence of trabeculations, pouches, etc. *Urinary examination;* especially with reference to the character of the infection, besides the ordinary tests.

Having then determined as accurately as possible the conditions present, a plan of action is mapped out: as to whether a Bottini operation or a prostatectomy be preferable, and if the former, what blade should be chosen, in what directions should cuts be made, and what should be their length.

The following cases, including several forms of hypertrophy, give in detail the operation found applicable to each and the length of blade chosen. They demonstrate, I think, the *raison d'être* of the new combined cautery incisor, and its practical value. The work with this instrument being of recent date unfortunately prevents our showing the ultimate result obtainable, as several months must generally elapse before the full effects of the operation are secured.

CASE I.—J. N. M., age 71, had been suffering with urinary trouble for 4 or 5 years. During this time urination became steadily more difficult and more frequent until he now voids every 1½ hours, night and day.

Examination showed slight, but definite, enlargement of the prostate, which was much harder than normal, but not nodular. The cystoscope showed a small median transverse bar and a slight intravesical projection from the lateral lobes, but there was really very slight intravesical enlargement of the prostate. With a finger in the rectum a very slight increase in thickness over the normal was felt between it and the instrument in the prostatic urethra. The bladder, however, showed very definite effects of obstruction, viz., considerable trabeculation and pouch formation, a residual urine of 90 c. c., and a capacity of only 250 c. c. *Remark:* We evidently had to deal with the so-called small sclerotic prostate, furnishing moderate but definite obstruction and a bladder hypertrophied and somewhat contracted. The very slight enlargement and the small amount of prostatic tissue beneath the urethra made us afraid to use Freudenberg's instrument. A thorough prostatectomy would have been impossible, and as the case appeared to be in need of the Bottini operation, we persuaded the patient to wait until the arrival of our new incisor, so that we might use a smaller blade.

On May 31, 1901, a Bottini operation was performed with blade No. 2 of our instrument, which blade seemed to suit the case exactly. Three cuts were made: one posterior, 2 cm. long; and two lateral, the right 2½ cm., the left 3 cm., at right angles to the posterior [see diagram]. The instrument was used at a high heat; time, about 1 cm. to the minute; the operation done under control of a finger in the rectum. It was evident that a larger blade would probably have cut through the posterior capsule of the prostate.

The convalescence of the patient was as usual: difficult urination for the first few days and after that a gradual improvement.

The ultimate result was a complete relief of prostatic obstruction, micturition free, residual urine nil.

CASE II.—F. E. B., age 34, presented himself on June 30, 1901, complaining of bladder trouble. The patient had had nocturnal incontinence of urine up to the age of 14, and after that he always voided urine much too often. Seven years ago cystitis developed, and a calculus was discovered and removed by suprapubic cystotomy. The fistula did not

heal till eight months afterwards, and cystitis has persisted ever since. On admission he passed his urine about 6 times a day, generally with pain referred to the neck of the bladder.

Examination.—Patient was a rather neurotic young man. The urine is cloudy, acid and contained phosphates, pus cells and bacilli. The prostate examined by rectum was slightly enlarged, considerably indurated at the upper end of each lobe. The seminal vesicles were both indurated and closely bound to the upper end of the prostate. The fluid expressed from the prostate and the vesicles by massage shows pus cells. A rubber catheter was passed into the bladder, but met some constriction of the prostatic orifice. The patient had just voided, but a residual urine of 220 c. c. was found. The bladder capacity was 500 c. c. The cystoscope showed a marked trabeculation of the bladder wall, a considerable thickening of the interureteral bar, and behind it a deep pouch in which was a considerable collection of sand and small calculi, white in color.

Examination of the prostatic orifice revealed a definite thickening of the median portion in the form of a transverse bar, and behind it a fairly deep bas fond. There was no intravesical enlargement of the lateral lobes, but the entire prostatic orifice was irregular and showed numerous granulations.

Remark.—Although the patient was a young man, he had unquestionably an enlargement of the median portion of the prostate, which was causing considerable obstruction to urination, as shown by the trabeculation and pouch formations in the bladder and the presence of 220 c. c. residual urine. The prostate was undoubtedly chronically inflamed, but the enlargement while probably inflammatory in origin was unquestionably causing trouble, and in our opinion demanded a Bottini operation. The prostate, however, was so small that it was out of the question to use the ordinary Freudenberg blade, so that patient was asked to wait until our instrument could be completed. In the meantime he was put upon bladder irrigations and given urotropin internally.

On September 13, 1901, examination showed considerable improvement in his cystitis, but the urine was still purulent. There was still 220 c. c. of residual urine present. Cystoscopic examination showed an improvement in the inflammation of the mucous membrane, and much to our surprise the considerable mass of small calculi which was previously found had disappeared. A very careful search was made with the cystoscope, but no calculous deposit could be found anywhere. There was still present the definite transverse median bar with a pouch behind it, and the bladder wall was still trabeculated. Accordingly the Bottini operation was performed, using blade No. 1 and making a single posterior cut through the median bar 2 cm. in length. There was some hemorrhage following this cut. After the operation the patient experienced considerable discomfort for a few days, but since then his condition has continued to improve.

It was intended to make three short cuts [see diagram] through the median bar with the small blade, but a burning out of some of the electrical connections in the hospital after the first cut had been made prevented the others being made.

Now two months have elapsed since the operation, his condition is much improved and the residual has dropped to 150 c. c. Unless this disappears soon we shall make the two other cuts through the median bar as originally intended.

Case III.—G. T. H., age 73, admitted Sept. 9, 1901, complaining of prostatic hypertrophy and catheterism. Urinary difficulty began soon after the age of 50, but did not get severe until about 1 year ago, when micturition became quite difficult, and the patient had to get up 2 or 3 times at night to urinate. About 10 months ago he had to resort to a catheter, which he has used ever since, being unable to void any urine naturally. He has had several attacks of inflammation of the bladder, and both testicles have been the seat of abscesses during the last 6 months. He now catheterizes himself regularly three times a day, and suffers very little discomfort, but the passage of the instrument is often quite difficult.

Examination.—Strong, healthy looking man, arteries slightly thickened, small nodules in both epididymes. Prostate markedly enlarged, about the size of a large orange, left lobe much larger than the right. The median furrow is deflected towards the right. The upper end of the prostate is hard to reach. The consistence is smooth, soft, not tender. Urine, acid 1014, not very cloudy, microscopically, numerous pus cells and bacilli.

Cystoscopic examination showed a very marked intravesical enlargement of the left lateral lobe, considerable enlargement of the median bar, and a lesser enlargement of the right lateral lobe, with a small rounded mass between the two lateral lobes in front. There was a very deep bas fond behind the prostate, and the bladder was very much trabeculated and inflamed. The blade of the Freudenberg instrument would have been perfectly suitable for this case.

A Bottini operation was done under chloroform, blade No. 3 being chosen. This blade is of the same size as Freudenberg's. The posterior cut was 3¼ cm. long, right lateral cut 3¼ cm. long, left lateral cut 3½ cm. long [see diagram]. The operation was done under the control of the finger in the rectum. Hemorrhage moderate and patient in splendid condition at end of operation. 1000 c. c. submammary infusion of salt solution was given as a prophylactic against uremia. The patient made a rapid convalescence, required catheterization only 3 or 4 times after the operation, and very soon began to void urine naturally. His condition since then has steadily improved, until now the interval between urinations is every 2 hours during the day and longer at night. His general health has improved wonderfully, he has gained 12 lbs. in 2 months, and will apparently get a good result.

Case IV.—E. W. S., age 63, admitted Sept. 13, 1901, complaining of enlarged prostate and catheterism. Urinary trouble began 4 years before with difficulty and frequency of urination, which at times had become so bad he had to use a catheter. For the past three months has had to use

catheter three times a day, and has not been able to pass any urine naturally. For the last four years the patient has suffered from diabetes mellitus, which has been somewhat controlled by dieting.

Examination.—Large, healthy looking man. The rectal examination showed a very large hypertrophied prostate, left lobe apparently larger than the right, consistence firm, but not nodular. Urine removed by catheter was acid, slightly cloudy, contained both albumin and sugar, and under the microscope showed pus cells and bacilli. After six days of diabetic diet there was barely a trace of it to be found. A rubber catheter entered the bladder with difficulty. The bladder tonicity was only moderately good, and the capacity about 500 c. c. The cystoscope showed a marked intravesical enlargement of the left lateral lobe, which projected into the bladder as a large rounded tumor, a moderate enlargement of the median portion, and a very slight enlargement of the right lateral lobe. Behind the prostate was a very deep bas fond in which the ureters could not be seen. The bladder was considerably trabeculated and inflamed.

Sept. 19, 1901. Bottini operation, under cocaine and morphia. On account of the considerable size of the prostate, blade No. 3 was used, and as the left lateral lobe was much larger than the right, a much longer incision was made on that side. The posterior median cut was 3½ cm. long, the left lateral 3½ cm., and the right lateral 2½ cm. [see diagram]. Time taken, 1 cm. to 1 minute. Instrument used at a white heat. There was very little hemorrhage following operation, and very little pain caused, the anesthetic being very efficient. Immediately after the operation the patient voided urine naturally, and has never been catheterized since. For the first few days there was considerable vesicle spasm.

On Oct. 2, 1901, 13 days after the operation, the following note was made: Patient now passes his urine about every 2 hours in a large stream and without pain. There is no dribbling. Residual urine 140 c. c. Urine, acid, quite purulent, pus cells and cocci present. Sugar is still present in considerable amount.

In a letter dated Nov. 5, 1901, the patient reports that he had not used a catheter since operation, that he urinates once during night and 4 times during the day, that his residual urine is less than 50 c. c., that micturition is free, and the vesical inflammation greatly improved.

CASE V.—J. P. A., age 71, referred to me by Dr. Finney on Sept. 28, 1901. The patient gave a very long urinary history, which began with difficulty in micturition 11 years ago, when a stone was found and removed by a surgeon through a suprapubic opening. For two years following this he had a suprapubic fistula, which was finally cured by his taking up catheter life in 1895. Castration was then done by another surgeon, and several weeks later another suprapubic to remove another stone. During the next year the stones reformed and were crushed by a third surgeon. After that he was free from pain for a while, but had to use a catheter. Stones soon appeared again, and during the next 12 months 4 separate litholapaxies were done. In 1897 still another surgeon did a suprapubic operation and removed stones, and at the same time removed by means of the Rongeur forceps a moderate-sized median lobe which was still present (despite the castration). After this operation, for the first time the patient was able to go without the use of the catheter, but micturition has been too frequent.

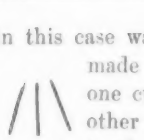
Status Presens.—Patient on admission complained of irritation of the bladder. He urinated every 2 hours during the day and twice during the night, but had no pain or discomfort during urination. Rectal examination: The outlines of the prostate were easily made out, and a little larger than normal. In the median line the prostate presented a slight but distinctly abnormal rounded mass. The lateral lobes were apparently much atrophied and sloped away from the central mass, which replaced the median groove and notch. The whole diameter of the prostate was half as large again as normal, the consistence of the lateral lobes soft and flabby. Urine, acid, 1022, containing pus cells, bacilli and cocci.

Cystoscopic examination: Rubber catheter met an obstruction about 7 inches from the meatus, but a silk one passed with ease. Patient had just voided, but 320 c. c. of residual urine was found in the bladder. Cystoscope showed two fairly large stones in a pouch behind a considerably hypertrophied interureteral bar. The mucous membrane of the bladder was much inflamed, but not markedly trabeculated, and there were no ulcers to be seen. Examination of the prostatic orifice showed a small but definite transverse median bar behind which there was a shallow bas fond. There was no intravesical enlargement of the lateral lobes to be seen, and there were no sulci between the lateral lobes above, nor between them and the median bar.

Remark.—The castration had removed the enlargements of the lateral lobes, but the median lobe persisted after that. The removal of this through a suprapubic opening allowed the patient to urinate without the use of a catheter, but there still remained a definite transverse bar at the median portion (the base of the middle lobe) which continued to act as an obstruction, 320 c. c. of urine remaining in the bladder after micturition. It was evident that after litholapaxy a Bottini operation should be done to remove this obstructing bar, but the amount of tissue felt beneath the instrument in the urethra was so slight that it was decided to use the smallest blade of the incisor.

On Oct. 17, 1901, under cocaine and morphia, litholapaxy was done, and followed by a Bottini operation. The crushing and evacuation of the stone was easily accomplished after placing the patient in the Trendelenburg position. The largest stone was one inch in diameter. All fragments were sufficiently crushed at the first introduction of the lithotrite to be removed by evacuation afterwards. After all debris had been removed, the bladder was washed clean, cocaine again inserted into the bladder and urethra, washed out after three minutes, and a Bottini operation performed. For this purpose blade No. 1, which

in this case was 8 mm. high, was used. Three cuts were made through the median bar, each 1½ cm. long, one cut being in the median line posteriorly, the other two cuts were made at angles of about 50° to the median cut [see diagram]. The operation was done with the forefinger of the right hand in the rectum pushing the prostatic bar into the angle of the beak of the instrument. This was done because it was feared that the length of the beak in the bladder would so depress the trigone and bar of the prostate that the knife would not penetrate it for its full depth.



The patient stood the operation well; anesthesia quite good; very little hemorrhage. He was unable to void his urine afterwards, and had to be catheterized three times in the next 24 hours. When seen a week after the operation he was voiding urine quite freely and the residual had dropped from 320 to 150 c. c. and he was already feeling greatly improved. He attended his office on the fourth day after the operation.

Condition one month after operation: Steady improvement, residual now 125 c. c., sometimes more. Bladder still large and weak in tone, but condition improving.

Nov. 21, 1901. Bladder capacity 400 c. c., tonicity considerably improved; residual, however, 175 c. c.

Case VI.—J. A. B., age 70, admitted Oct. 18, 1901, complaining of enlarged prostate and catheterism. His urinary trouble began ten years before with difficulty and frequency, which soon became so aggrevated that he began the use of a catheter, which he has used continuously up to this time. For the past 7 years he had been unable to void any urine naturally, and when admitted passed a catheter about every two hours during the day and about every three hours during the night, using a very large rubber catheter. Examination showed a very large, hard prostate and a considerable dilatation and lengthening of the urethra just in front of the prostate. The cystoscope revealed a moderate-sized stone in a pouch behind the prostate, and a very much inflamed and trabeculated bladder. There was present a considerable intravesical outgrowth of the prostate, which appeared as a collar-shaped enlargement, both lobes and the median portion being hypertrophied, the left projecting farthest into bladder. Behind the median bar was a deep pouch. The bladder capacity was rather small. The urine, which was obtained always by catheter, contained many red blood-corpuscles, pus cells and bacilli, and was acid in reaction.

On Oct. 23, 1901, litholapaxy was done under chloroform. The operation was begun under cocaine, but chloroform had to be used on account of pain. The largest diameter of stone grasped by the instrument was 2 cm. The crushing and evacuation were both difficult on account of the great hemorrhage caused and the trabeculated condition of the bladder. Patient stood the operation well and was very much more comfortable afterwards, but still required catheterization.

On Oct. 26, 1901, a Bottini operation was done under cocaine 4% and a hypodermic of ¼ gr. of morphia. Blade No. 3 was chosen as the proper size for all of the cuts, of which three were made, one posterior through the median bar 2¾ cm. long, a right lateral 2½ cm. long, left lateral 3 cm. [see diagram]. The duration of cuts was about 1 cm. to 1 min. and a high heat was used on the blade. There was very little hemorrhage following the operation, and immediately afterwards the patient voided urine.

Patient made a rapid convalescence, voiding his urine freely immediately after the operation and never after required catheterization, although he had led a catheter-life for 7 years.

On Nov. 7, 1901, 12 days after the operation, he reported that he was rapidly improving, that he passed his urine once every three hours without any straining and was free from pain. A catheter passed 4 weeks after operation finds no residual urine, and the cystitis considerably improved.

Case VII.—J. M. D., age 73, admitted Oct., 1901, complaining of hypertrophy of the prostate and catheterism. Urinary trouble began about 7 years ago with difficulty of urination. A little later retention of urine became complete. He then began to use a catheter, and has had to use it ever since, never being able to pass any urine. He has remained in fairly good health, has had very little inflammation of the bladder, and now has to pass a catheter about every 4 hours, twice during night. Increasing difficulty in introducing the instrument of late has driven him to the operation.

Examination.—Large, healthy looking man, arteries slightly thickened, heart and lungs apparently normal. Small hydrocele of right side. Prostate very much enlarged, about the size of a moderate-sized orange, lateral lobes about equally enlarged, contour round, smooth, consistence hard. Seminal vesicles indurated, but not nodular. A rubber catheter met obstruction 9½ inches from meatus. The bladder capacity was 400 c. c., tonicity rather poor. Urine acid, slightly cloudy, and contained pus cells and bacilli. The cystoscope showed a very markedly trabeculated bladder with numerous small pouches. Behind the prostate was a very deep bas fond in which the ureters could not be seen. There was considerable inflammation of the mucous membrane. Both lateral lobes and the median portion were very much enlarged, presenting a large collar-shaped intravesical hypertrophy around the urethral orifice, which projected well out into the bladder cavity. Growing from the upper portion of the lateral lobes, especially the left, were numerous small villi, which floated in the fluid but caused no hemorrhage. There was no ulceration of the surface of the prostate.

Oct. 28, 1901. Bottini operation, cocaine and morphia. Blade No. 3 was chosen. Four cuts were made, one in the median line posteriorly across the median bar 3¼ cm. long, one right lateral cut 3 cm. long. Through the left lobe 2 cuts were made, one lower oblique at an angle of about 75° to the median posterior cut 3¼ cm. long, and an upper

oblique cut at an angle of about 130° to the posterior median cut also 3¼ cm. long. The direction of these cuts is best shown in the accompanying diagram. Patient stood operation well. There was very little hemorrhage, and anesthesia was quite good. Time occupied was about 1 cm. to 1 min. For the first 24 hours after operation the patient voided urine with considerable ease, after that it became more difficult, the bladder becoming irritable and catheter had to be used for six days. After that patient began to void without the use of a catheter.

Condition three weeks after operation: Patient voids about every hour, but sometimes 2½ hours elapse between urinations. The vesical inflammation is improving, and its capacity increasing gradually. The catheter on which he depended for seven years has not had to be used for two weeks.

On Nov. 21, 230 c. c. of urine was voided at a time with an interval of two and a half hours. Urination fairly free, stream large. Residual urine, 10 c. c.

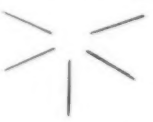
Dec. 13. Patient voids urine about 6 times in 24 hours, in amounts varying from 150 to 210 c. c.

CASE VIII.—S. M. A., age 56, admitted Oct. 28, 1901, complaining of frequency of urination. His prostatic trouble began 2½ years before with difficulty of urination. Since then micturition had become gradually more frequent and difficult, and one year before he had begun the occasional use of a catheter. On admission he complained of a dull pain at the beginning of urination, which occurred every 2 or 3 hours during night and day. He had suffered considerably with inflammation of the bladder.

On examination patient was found to be a man in fairly good health. The prostate on rectal examination was found to be slightly enlarged, soft in consistence, contour smooth and round, and both lobes of about the same size. The seminal vesicles were not indurated. The urine was cloudy, specific gravity 1017, pus cells and bacilli were present in considerable number. A rubber catheter passed with some difficulty, owing to obstruction in prostatic urethra. Residual urine 185 c. c. (another examination 3 weeks later showed a residual of 375 c. c.). The bladder capacity was between 500 and 600 c. c.; tonicity fair. Cystoscope showed a small median bar which joined, without intervening sulci, with two very slight intravesical enlargements of the lateral lobes. Behind this median bar was a definite, but not very deep, bas fond in which the ureters lay, rather close up to the prostate. The interureteral bar was considerably enlarged and behind it was a rather deep pouch. The posterior wall of the bladder was very greatly trabeculated, and between some of these trabeculæ small round and oval openings were seen which connected with extravesical pouches. About 1 inch behind the left ureter a very considerable diverticulum with a large round opening into the bladder was seen, and the cystoscope was introduced into this for some distance, and a cystoscopic examination of the diverticulum made. With a finger in the rectum and the cystoscope in the urethra the amount of prostatic tissue between them was found to be very little thicker than normal; more than in Cases II and V, but much less than usual in prostatic enlargements.

The rectal examination and cystoscopic examination both showed only a slight enlargement of the prostate, but the considerable residual urine and the marked evidences of obstruction as shown by the trabeculation and pouch formation in the bladder wall made it evident that there was considerable hindrance to urination. The prostate was so small that prostatectomy would have been very difficult, although the patient was in splendid shape for any operation, and the ordinary Freudenberg instrument would undoubtedly have been dangerous to use on account of the danger of penetrating the capsule of the prostate. Blade No. 2 of our instrument appeared to be the proper size to be used with cuts not longer than 2 cm.

On Nov. 20, 1901, a Bottini operation was performed under cocaine and morphia. Blade No. 2 was used in accordance with the cystoscopic and rectal examinations as stated above; 5 cuts were made as shown in the diagram. One median-posterior and two oblique on each side, one at an angle of 75° to the median posterior, and the other at an angle of 120°. Each cut was made 2 cm. in length. Patient stood operation well. There was very little hemorrhage from the cautery cuts. The catheter was not required after the operation.



On the day following the operation there was a temporary suppression of urine, which was relieved by subcutaneous infusions and digitalis.

Dec. 13. Patient has done well. Urine voided freely, often 300 c. c. at a time. Residual urine 0. Cystitis improving. Result excellent.

Reviewing the eight cases reported in full, we find four cases (III, IV, VI, VII) in which blade No. 3 was used. All of these were fairly large hypertrophies of both lateral lobes and median portion, and were suitable cases for Freudenberg's instrument.

In two cases (I and VIII) blade No. 2 was used. In both of these the prostate was very slightly larger than normal, as shown by rectal, instrumental and cystoscopic examinations, but in both of these cases there was marked evidence of obstruction and the cases urgently needed operation. In both cases, however, incisions made with Freudenberg's instrument would probably have penetrated beyond the confines of the prostate, but the operations were performed safely with blade No. 2 of our instrument.

In two cases (II and V) blade No. 1 was used. In both the obstruction was caused by a very small median bar, associated with complete atrophy of the lateral lobes (after castration) in one case and lobes of normal size in the other. In these cases the amount of tissue beneath the instrument was so small that we feared to use even blade No. 2. In another case (not here reported) the enlargement consisted

in two very large lateral lobes, associated with a complete absence of median bar, the urethra skirting the posterior surface of the prostate and the amount of tissue between the rectum and a sound in the prostatic urethra being very small. In this case we used blade No. 3 for the lateral lobes and blade No. 1 for the posterior cut.

FIG. 8.

I have not as yet used blade No. 4, and hardly think it will often be necessary except to attack a single very great hypertrophy of one lateral lobe. I have, however, seen several tremendous general hypertrophies in which it would have been necessary.

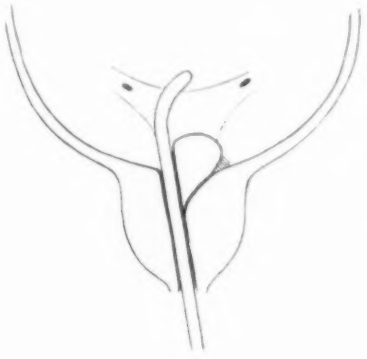


FIG. 9.

As to the efficacy of the Bottini operation, of which I was myself at first very skeptical, my experience (now of 41 operations) forces me to testify decidedly in its favor.

In 41 cases I have had three deaths, all men in very bad condition before operation, and two with pyonephrosis. Fifteen patients were over seventy years of age, three over 80, and among these there have been no deaths, and all but one have been cured of the prostatic obstruction. Of thirteen patients who had to use the catheter, there is only one who still requires it, and this one is considerably improved. Some of my cases are of too recent date to show the ultimate results, and these I will reserve for a later publication. I am still, however, of the opinion (from an experience of 15 prostatectomies) that in certain cases, *e. g.*, men between 45 and 60, in good condition, and with easily enucleable enlargements, a complete prostatectomy is a very safe operation, and certain as to lasting results, though I must say the effects of the Bottini operation seem to be also permanent. Time, careful study of cases (especially with the aid of the cysto-

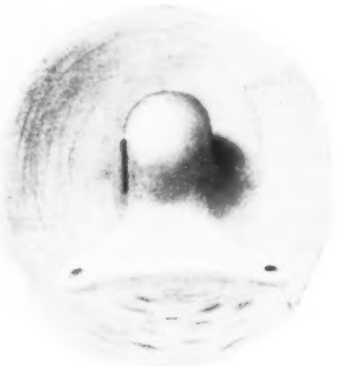


FIG. 10.

scope) and long-continued observation after operation can alone determine the applicability and the limitations of the principal operations for the treatment of prostatic hypertrophy.

In closing the paper I cannot too strongly urge that the

FIG. 11.

Bottini operation should be performed in accordance with the character of the prostatic obstruction as found by exhaustive examination as previously outlined. There is no doubt but that a perfunctory performance of the operation with one blade for all cases, and one cut directed posteriorly and one laterally on each side, while perfectly satisfactory in a large number of cases, is insufficient in some and dangerous in others.

As shown by the writer in another paper,[1] when a decided median lobe (more or less pedunculated) is present, the ordinary operation is entirely inadequate, as the posterior

[1] Monatsberichte für Urologie, Jan., 1901.

cut will generally pass to one side of the median lobe and leave it to continue its obstructive work [see Figs. 8, 9, 10].[2] If, however, the cuts be so made as to pass obliquely across the base on each side of this projecting lobe,[3] I have shown that this lobe may be dropped back out of the way and a rapid atrophy induced by thus cutting off most of its blood-supply [as in diagrams, Figs. 11, 12, 13]. This has been abundantly proved in five cases, some of which were entirely unaffected by the usual three incisions and the prostatic obstruction immediately removed by the incisions described above.

The cases outlined above serve to show the selection that may be made in some forms of hypertrophy as to the size of blade to use, and as to the length of incisions, their number and direction. No two cases are alike, and each should be a study unto itself.

As a rule, the usual three incisions—one posterior and two lateral—are entirely sufficient for most cases, especially those of moderate hypertrophy, where with more incisions the danger of causing a slough, too large to be passed per urethram, is considerable. The same rule applies to middle lobe cases: unless the median enlargement is considerable the single posterior incision should be preferred as free from all chance of completely amputating the middle lobe, and leaving it to act as a foreign body in the bladder. In the choice as to the length of incisions and the size of blade to use, there is considerable latitude, and it should always be based on a careful study of the conditions present and controlled by rectal touch.

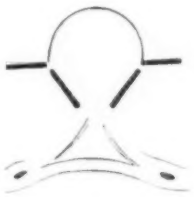


FIG. 12.

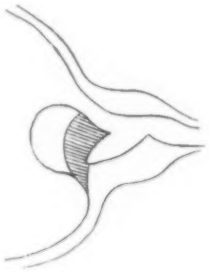


FIG. 13.

[2] To be more explicit: Fig. 8, shows the Y shaped urethra which is present in these middle lobe cases, and Fig. 9 shows how a metal instrument that has been introduced into the bladder will pass to one side the middle lobe, and not remain on top of it. Fig. 10 illustrates a case in which I performed the usual Bottini operation with no result, and a subsequent suprapubic cystotomy showed the posterior cut on one side of the middle lobe as shown in Fig. 10.

[3] This is accomplished by the following manoeuvres: Introduce incisor, draw beak up against anterior portion of the prostatic orifice, rotate instrument 180° (hugging the prostatic orifice all the while.) This will bring beak into sulcus to one side of middle lobe. Carry the rotation 45° further and beak will lie obliquely across the base of the middle lobe, ready for the first cut, Fig. 11. By reversing these movements the cut on other side of middle lobe may be similarly performed, and then the two lateral cuts made, Fig. 12. The result is shown in Fig. 13, a diagram from an autopsy specimen.

THE DISTRIBUTION OF ANOPHELES IN THE VICINITY OF BALTIMORE.[1]

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In the spring of 1901, at the suggestion of Doctor Thayer, a study of the distribution of *Anopheles* larvæ infesting the ponds and streams in and around the city of Baltimore was undertaken. Thayer and Lazear (1) had already found adult *Anopheles* at Sparrows' Point, a suburb of Baltimore, in 1899. The larvæ, however, had never been found.

Our search for the larvae ultimately extended over the whole of the city and nearly all of its suburbs and neighboring villages. These included Sparrows' Point, Chesapeake Mills, River View, Orangeville, Gardenville, Dickeyville, Windsor Heights, Roland Park, Calverton Heights, Brooklyn, Middle River and Back River.

Along these latter rivers, which are tributaries of the Chesapeake Bay, there are scattered a number of club houses, hotels and pleasure shores, where city people go to fish, shoot and enjoy an outing during the summer season. These places, therefore, are usually rather densely populated from June until October.

It was very interesting to note that a very defini.. could be drawn across the city, above and to the west of which the larvæ of *Anopheles maculipennis* were rarely found, and below and to the eastward of which few *Anopheles punctipennis* were ever taken.

The larvæ of *Anopheles punctipennis* did not appear until about the middle of July, while the first *Anopheles maculipennis* were obtained on June 20.

Wherever or whenever *Anopheles* larvæ were taken the approximate number of them per cubic metre, if possible, was always estimated for the time and the place. This method, of course, applied to a given body of water, gives no notion as to their number and distribution. For, in the backwater of the Chesapeake Bay, about one hundred and fifty larvæ of *Anopheles maculipennis* were found in one cubic metre, and not another larval form was found within a radius of one mile.

[1] Read at the meeting of the Johns Hopkins Medical Society, Dec. 16, 1901.

The larvæ were captured throughout the summer until October 22 in the backwater of the Chesapeake Bay and Patapsco river seventy times; twelve times in stagnant pools; in slowly flowing, almost quiet brooks and pools twenty times. In marshy ground with very small scattered patches of water, larvæ were taken five times. One *Anopheles maculipennis* was found in a rotting log filled with rain water.

The common bullrush or cattail, *Typha latifolia*, was a shelter beneath which *Anopheles maculipennis* was nearly always found. Neither species of *Anopheles* was ever taken in artificial receptacles such as boxes, basins, kitchen utensils, flower-pots or any such vessel which might contain water, although Drs. Cassidy and Bayne of Roland Park found *Anopheles punctipennis* in rain barrels.

Larvæ of *Culex* were found in the same bodies of water with *Anopheles* much more frequently than the results of other investigators would lead one to suppose. The larvæ of both *Anopheles* and *Culex* occurred together in all but ten cases above, only a few *Culex* in fifteen instances.

In eighty cases larvæ were found alive and thriving in the same places as fish. In several cases sunfish, perch, trout and gudgeons could be seen below the larvæ waiting for food of a larger sort. Twice it was our fortune to find boys fishing near the rushes where the larvæ were captured, and a snap-shot was taken by Dr. Eldred, of Sparrows' Point, who accompanied us on this excursion.

After several days of heavy rain, the young forms of *Anopheles* larvæ became very numerous. It was also noted that the water about the margins of petrolized pools contained larvæ when they were examined several days after a period of rainfall. In such cases the petroleum had collected toward the middle of the pool and appeared to be diminished in amount.

Although under natural conditions the larvæ seem to thrive very well in the presence of fish in some natural ponds and rivers, when we, however, attempted to breed larvæ in an aquarium in order to test this fact, it was quickly found that the larvæ were all eaten by the fish. This was so even when [illegible] and perch were placed in the aquarium. Sunfish and perch only were used for this experiment. Both species devoured the larvæ, even when well supplied with other food.

Of forty *Anopheles* imagines captured, ten of which were *Anopheles punctipennis*, and thirty *Anopheles maculipennis*, not one contained sporozoites or zygotes. Only eight of these, all maculipennis, were captured inside a house, the persons in the house being free from malaria.

The larvæ were usually collected in small bottles or fruit jars with loose screw tin tops, through which sufficient air passed to keep the larvæ alive. In transporting the larger and more nearly mature forms we often killed them by jolting during transportation. The smaller forms rarely died in this way. Nuttall, Cobbett and Strangeways-Pigg (2) call attention to this fact.

An ordinary white porcelain saucer was employed for dipping the larvæ from their pools, and in order to avoid transferring an unnecessary amount of water into the bottles with the larvæ, a long pipette with a rubber bulb attached was used to take up the larvæ from the saucer, as recommended by the above writers (3).

When it became necessary to wade out farther than boots or our bare feet and legs could take us, the saucer was placed in the bottom of a long-handled, shallow crab net. A dip could be carefully made with this and any larvæ easily detected over the white surface of the saucer.

The color of the larvæ was usually black, but this was not invariably the case. In four different pools with clear shallow water over a fine sandy bottom they were almost the color of crayfish. In two other sluggish streams with a fair amount of vegetation growing in and around the margins, the larvæ showed a distinct greenish tint, even more noticeable after being taken from the stream. The green color did not seem to be due to food within the digestive tract.

Occasionally, in a mass of larvæ, about one-quarter of them showed a quadrangular white area in the mid-dorsal region of the thorax and the third abdominal segment. This was only observed in the *Anopheles punctipennis* series. Dr. Cassidy first called attention to this.

The larvæ are most commonly found around or near the margins of pools, etc. If there are islands of algæ, *Typha latifolia* or other vegetation in the middle of the water, larvæ are frequently at the bottom, in the mud which accumulates about or near the roots of the rushes.

Although, as has often been stated, any passing breezes blow the larvæ towards the margins of the ponds, the fact that they are on the windward edge of the bank, as well as on the leeward side, and are also arranged in a radiating manner around the sides of artificial receptacles in which they are kept in the laboratory, cannot be accounted for by supposing that the wind causes them to take such positions.

By carefully observing the larvæ after they have been disturbed, it can be seen that their movements are made so rapidly and always tail first that they are not brought to a halt until the impact of their tails against the sides of the vessel. When all is quiet again, they may be seen ranged about the sides, radiating towards the centre of the vessel, head first. The methods of differentiating larvæ of *Anopheles* from the larvæ of *Culex* are now so well known that any detailed information is quite unnecessary. It may be obtained from the book of Dr. L. O. Howard (4) or the articles of Nuttall and Shipley (5).

About the average number of *Anopheles* larvæ brought to the imago stage was five in every twenty, or 25 per cent. The average length of the larvæ captured was 2.9 mm., although they ranged in size from 1 mm. to 9.2 mm.

The average time for the larvæ to become pupæ was twenty-two days in July and August with an average temperature of 28.5°, and taken during the day.

Two days was our average time for the pupæ to cast their shells and become imagoes. It was very difficult to keep the adult *Anopheles* in confinement even with the most careful attention. One week was the average duration life of the

Chesapeake Mills.

Sparrows Point.

Point midway between Sparrows Point and Chesapeake Mills.

Inlet of Chesapeake Bay at Sparrows Point. Fishing among the cat-tail bullrushes.

adults during July and August, and it seemed easier to keep *Anopheles maculipennis* alive in the cages than *Anopheles punctipennis*. One *Anopheles maculipennis* was kept seventeen days, the longest period of any adult in our series during these warm months. Later in the fall as the average daily temperature fell, it was very easy to keep the adults for sixty days with careful attention.

The larvæ were always kept in a large, well-lighted and ventilated laboratory having windows facing east, north and west. The receptacles which contained the larvæ were of glass (and either circular, cylindrical or globular in shape). They ranged from ten to thirty centimetres in diameter and from five to ten centimetres in depth. Similar vessels were also used for holding the food. As the larvæ increased in size they were placed in larger glass jars and over these was placed fine gauze mosquito netting to prevent the egress of mosquitoes and the ingress of house-flies. Two vessels were kept in a cage made of wire screening of closely woven meshwork. This box was thirty-four centimetres square and had been previously used for caging mosquitoes by Thayer and Lazear.

Experiments relating to the food of the larvæ were tried with the following results. Thus, as suggested by Manson (6), rice was added to the water in two instances, and the rapid growth of bacteria which followed completely cut off the supply of air for the larvæ by the formation of a thick, gelatinous film of zooglea over the surface of the breeding jars. The larvæ were all killed.

Cultures of *B. lactis aerogenes, B. violaceus, B. prodigiosus, Penicillium* spores, *B. subtilis* all multiplied rapidly, so rapidly, indeed, that the larvæ could not use them as food, but were in turn killed by them or by their products formed from them.

The larvæ thrived best upon diatoms, *Spirogyra* and other algæ and protozoa, which are usually found in the natural habitat of the larvæ, and can be collected along with them. It was found that supplies of algæ could always be kept in sufficient quantities to last for days if they were cultivated and thrown in aquaria containing no mosquito larvæ. This was very convenient, inasmuch as it became necessary to change the water frequently in warm weather and consequently required considerable numbers of them to furnish food for our embryo mosquitoes.

When the imago left its pupal shell, immediate provision was made to keep it supplied with necessary food. If ripe fruit could not be at once obtained, one of the writers permitted the females to feed from his blood until fresh bananas or oranges could be furnished.

Pieces of freshly cut banana or orange were kept in the cages when adults were present, and occasionally the females were allowed to have some human blood. The females seemed to bite as well during the day as during the night.

Six *Anopheles maculipennis* were permitted to bite the blood of patients suffering from the aestivo-autumnal form of malarial fever, in whom crescents had already been demonstrated. The method employed was as follows: One of the newly hatched mosquitoes was captured by placing a wide-mouth test tube over the insect while at rest, in the manner advised by Thayer (7). The mosquito would rise to the top of the tube after a time, and a cotton plug was then quickly placed over the mouth of the tube. The lobe of the patient's ear was then carefully cleansed with alcohol and allowed to dry. The cotton in the mouth of the tube was then carefully replaced by the lobe of the ear. This was best done beneath the bed clothing, although it was also successfully done in one instance in the open light of day. The female *Anopheles* bores her proboscis into the lobe of the ear practically without the knowledge of the patient. Once this occurred without disturbing the patient, a sleeping boy of sixteen years. In only one instance was any complaint made, and this in the case of an hysterical female.

After *Anopheles* had bitten the patient, it was placed in an incubator at a temperature of thirty degrees centigrade and allowed to remain there for five, six, seven or eight days.

In none of the six cases were we able to demonstrate zygotes or sporozoites in the stomach wall, body cavity or salivary glands. Fresh preparations were always employed and the usual method (8) for dissecting the mosquitoes was carried out. A Leitz one-twelfth immersion lens was used in the microscopic work. The mosquitoes when examined were placed in normal saline solution on an ordinary slide.

The adult *Anopheles* was often caught flying near the pools where larvae were found. This was observed only about dusk. During the day, *Anopheles* was rarely found and then usually at rest unless disturbed. The only imagines caught inside of dwellings were females, swollen wtih the blood they had imbibed. They were always sluggish when disturbed and easily captured on the wing. *Anopheles punctipennis* was observed to hatch out often during the day.

In all, *Anopheles* were collected one hundred and six times in forty-six different places; *Anopheles* and *Culex* were found together ninety-six times. In fifteen cases *Culex* were few, only one, two or several more being present. Fish occurred in the same streams as the larvae eighty times. These cases all occurred at Sparrows' Point.

The inlets from the river and bay at Sparrows' Point have their borders filled with *Typha latifolia*. Among these rushes, hidden from their enemies, the larvæ of *Anopheles maculipennis* were found continuously from June the twentieth until October the twenty-second.

At Chesapeake Mills, about a mile from Sparrows' Point, stagnant pools and salty backwaters are likewise alive with the same larvæ. A chain of *Anopheles*-infested pools follows a line parallel with the tracks of the Pennsylvania railroad from Sparrows' Point to Chesapeake Mills. One other pool between Baltimore and Chesapeake Mills contained them also.

A clear, slowly-flowing brook near Towson yielded large numbers of *Anopheles punctipennis*. Other small pools of water in neighboring places also contained them. No adult were captured in houses but several males were taken from the thick, low foliage near the water.

A small run or brook near Govanstown, on the York Road, which flows over a limestone bed showed larvæ of *Anopheles punctipennis* in the water of gullies and holes left by the receding stream after a period of dry weather.

At Roland Park the larvæ were found in two stagnant pools thickly covered in places by a green scum (*Lemna* ?) (3). One of these pools contained myriads of *Culex* larvæ and was situated alongside the principal thoroughfare. *Anopheles* larvæ were also found by Drs. Cassidy and Bayne (who carefully worked over the region around Roland Park) in old receptacles containing water, in a rain barrel and in various pools and marshes. We found them in a stream not far from the railroad and also in two very clear ponds near a golf course and in the Country Club grounds.

A stream running through Windsor Heights and Walbrook contained a few *Anopheles punctipennis*, but no *Culex*.

At Calverton, *Anopheles punctipennis* was found only once in a stream of dirty water.

Brooklyn, Anne Arundel County, yielded several small streams with *Anopheles maculipennis* and a great number of *Culex*.

The Herring Run, Jones Falls, the Gunpowder River, Bush River, Middle River and Back River, were each carefully searched by one of us without success, and the entire surrounding country was threshed out as mentioned above.

It might be of interest to know that some cattle brought from Queen Anne's County on one of the excursion boats were observed to have mosquitoes hovering about them when taken aboard about eight o'clock one evening at Queenstown. There was one *Anopheles* among them, the species of which was not determined.

In conclusion, then, we may say:

First. With regard to the general distribution, that the breeding places of *Anopheles* are found in the suburbs to the north, east, south and west of the city. But that *Anopheles punctipennis* breeds in the higher sections of the neighboring country, namely, to the north and west; while *Anopheles maculipennis* is to be found where the country is lower and the water salty, namely, to the east and south.

Second. Since the bite of the mosquito is now known to be the source of infection in malarial diseases, the question of prophylaxis is largely one of exterminating these insects. This can only be accomplished by destroying the pools already infested with *Anopheles* and by preventing the formation of others. A moment's reflection will scarcely be necessary to show the difficulty of carrying out what is now at least, apparently a hopeless task. Innumerable pools of stagnant water fed by the ebb and flow of the tide of the Patapsco, in the low marshy country along the river front especially in the neighborhood of Sparrows' Point and intermediate places, offer an almost insuperable obstacle to the proper drainage of the infected districts. Nor does the filling in of the marshy places bordering on sluggish streams in other places present a more feasible solution to this difficult problem.

Third. In view of these facts it should be emphasized that other means must be adopted if the disease is to be stamped out. As Manson has well said: "In proportion as the liability to mosquito bite is diminished, exactly in the same proportion is the liability to infection reduced." Hence of special importance is the careful screening of doors and windows by wire gauze or mosquito netting as suggested by Celli. Where this cannot be done, fitting the beds with netting will offer security, inasmuch as most *Anopheles* bite at night. Again, persons already infected should be protected by screens to prevent infection of healthy mosquitoes and thus spread the disease broadcast; inasmuch as a patient having been infected in one place may carry it to another and infect the mosquitoes there.

Finally, cases of malarial infection should be reported to the city Board of Health just as are the contagious diseases; and thus enable precautions against the spread of malaria to be carried out under the proper supervision.

We again wish to express our thanks to Dr. Thayer for his kind suggestions and also to Drs. Cassidy and Bayne, of Roland Park, and Dr. Eldred, of Sparrows' Point, for much assistance.

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A NEW METHOD FOR THE DEMONSTRATION OF THE FRAMEWORK OF ORGANS.

By Joseph Marshall Flint, M. D.,

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(From the Hearst Anatomical Laboratory of the University of California.)

Although in recent years much interest has been taken in the study of the connective tissues, it is nevertheless true that our knowledge of these important structures has grown only by small increments. The results apparently have neither been commensurate with the importance of the questions involved nor the interest that has been taken

in them. Many anatomists believe, moreover, that the mesoblastic tissues as a whole have scarcely received the attention they deserved, in comparison with the relatively greater amount of work that has been done in their ecto- and endodermic neighbors. It seems probable, too, that the simple connective tissues may have a more important rôle in the general economy than the simple sustentacular function usually assigned to them. The probability of their association with certain physico-chemical phenomena of secretion, their arrangement to provide for certain degrees of elasticity, to meet the stress and strain of organs, their importance pathologically, are all suggestive facts which support this view. For example, recent work on the behavior of solutions and osmotic phenomena suggests the possibility that the basement membranes of glandular acini as well as the cytoplasm of the secreting cells may possess the property of semi-permeability. Now, when we consider the great results that have followed the application of the principles of physical chemistry to morphological and physiological problems, it does not seem improbable that we shall be able to revert to the older theories of secretion and show that part of these phenomena are merely expressions of simple physico-chemical laws, rather than the result of the activities of cells under the influence of secreto-motor nerves.

Many methods have, up to this time, been devised to show the framework of organs and the connective tissues of the body, among which may be mentioned those of teasing, selective staining, precipitation, maceration, and digestion. All of these methods have been, and indeed still are, valuable in the study of the connective-tissue framework of various organs and tissues, but there is little doubt that the most fruitful results have followed the use of the several destructive methods, of which tryptic digestion is perhaps the most effective. Ewald and Kühne[1] were the first to use this method in separating elastic fibres from the reticulated tissue of the lymph glands which they supposed were composed of collagenous fibrils. Mall,[2] in his study of the reticulated tissues undoubtedly made the greatest improvement in our technique by digesting frozen sections with pancreatin in order to show the reticulated framework of various organs. In this way he succeeded in digesting all of the cells and connective tissue corpuscles, leaving the white fibres and reticulum untouched. After the digestion and shaking to remove the cellular débris, these preparations were mounted and stained. Spalteholz[3] succeeded somewhat later, by means of trypsin, in digesting small pieces of tissue in bulk which had previously been fixed and hardened in graded alcohols or bichloride. Tissue thus prepared, sectioned in paraffin and stained with iron hæmatoxylin, gives very sharp and definite pictures of the connective-tissue framework. This procedure was very much simplified later by Hoehl,[4] who found that he could, after thorough fixation on the slide, digest thin sections which could then be stained and mounted. Still further improvements of Hoehl's procedure were made by Clark,[5] who stained and digested alternate sections, so that he was able to interpret more accurately by ordinary stained preparations the arrangement of the connective-tissue framework in digested sections.

Somewhat later[6] it was shown that the pictures obtained from the digested frozen sections and the method of piece or slide digestion were practically the same, all of the differences, apparently, depending on differences in the methods of preparation. The disadvantages of the Spalteholz method lay in the fact that, while the connective-tissue fibrils were firmly fixed in situ by the preliminary hardening, the sections were so thin that it was impossible to follow them for any distance. An adequate conception, therefore, of the course of the fibrils in three dimensions could scarcely be formed. By the use of Mall's method this difficulty was partially obviated, and yet the agitation of the sections necessary to free them from the cellular débris often dislocates the fibrils, so that one could not be absolutely certain of their course. Some method, therefore, was needed which would combine the good features of both of the others, one that would not only fix the fibrils absolutely in the position occupied during life, but would at the same time, show their course for a considerable distance in three dimensions. While working in Spalteholz's laboratory and using his method of piece digestion, the writer succeeded, by the use of the stereoscopic microscope and cleared pieces of tissue that had been previously digested in bulk, in demonstrating beautifully the framework of certain organs in three dimensions. The procedure, which is, of course, an extension of Spalteholz's method of piece digestion, may be briefly described as follows:

For the purpose of digestion, the pieces of tissue may be quite large, although in order to permit the free action of the proteolytic enzyme and to facilitate the extraction of the fats, it is scarcely wise to have them exceed 3 mm. in thickness. While it is possible to extract and digest pieces of tissue somewhat thicker than this, no real advantage is gained, inasmuch as the penetration of the stereoscopic microscope does not exceed this depth. It is best, perhaps, to harden fairly large blocks of tissue, and after the hardening to cut them into thinner slabs with a sharp razor, so as to have two nearly parallel plane surfaces on which to use the microscope. Excepting the thickness, the other dimensions are immaterial and can be as great as the nature of the tissue or the work demands. Of the various fixing fluids adapted to this procedure, the mixture of Van Gehuchten

[1] Ewald and Kühne: Verhandl. d. naturh. med. Ver. zu Heidelb. Bd. 1.

[2] Mall: Abhandl. d. k. S. Ges. d. Wiss., 1900 and The Johns Hopkins Hospital Reports, vol. I.

[3] Spalteholz: Arch. f. Anat. u. Phys. Anat. Abth., Suppl. Bd. 1897.

[4] Hoehl: Arch. f. Anat. u. Phys. Anat. Abth., 1897.

[5] Clark: Arch. f. Anat. u. Phys. Anat. Abth., 1898.

[6] Flint: Anatomischer Anzeiger. Bd. XVI, 1899; Contributions to the Science of Medicine, dedicated to Dr. William H. Welch by his pupils. Baltimore, 1900. The Johns Hopkins Hospital Reports, vol. IX, 1900.

is perhaps the best. It works rapidly, gives good cytological pictures and the chloroform it contains loosens up the fat and thus facilitates the subsequent ethereal extraction. The fluid is made as follows:

Glacial acetic acid	10 parts.
Chloroform	30 "
Absolute alcohol	60 "

Very good results can be obtained with the corrosive acetic mixture, by the use of the graded alcohols, but tissue must not be fixed in formalin, in fluids containing chromic acid or its salts, or those in which osmic acid is an ingredient. Trypsin is powerless to digest tissue that has been hardened in fluids containing any of these reagents. After the fixation it is best to dehydrate the tissue gradually in order to avoid any possible shrinkage. Moreover, great changes in the strength of the alcohols seem to render the digestion of tissue more difficult. After the dehydration is complete the tissue is transferred to ether, placed in one of the filter paper cups and then dropped into the receptacle of a Soxhlet apparatus and is extracted for 5 or 6 days continuously. In Leipzig, the experience with the Soxhlet apparatus had not been altogether satisfactory, and several explosions led them to substitute chloroform for ether in order to escape this danger. The chloroform, of course, does not burn, but at the same time does not seem to extract the fats as well as ether. To overcome this difficulty the Soxhlet apparatus can be placed in a hood and operated by means of hot water obtained from a Fletcher heater situated in another part of the room, or the heater may be placed in the hood and the ether apparatus erected in a sink. In this way all danger of explosions can be obviated and the apparatus may be operated day and night with perfect safety. Prof. Spaltcholz writes that he now uses an electric resistance plate to heat the ether flask, a method which is at once safe and economical if the electric current can be obtained. Another method which involves the use of electricity has been devised by Prof. O'Neill, of the Univ. of Cal., which is much simpler than the resistance method used in Leipzig. The ether flask is placed in a snugly fitting cylindrical roll of asbestos board. An ordinary electric light bulb, which generates sufficient heat to keep the ether boiling is then inserted in the cylinder beneath the ether flask. Most laboratories are, however, not wired so that the use of the Fletcher heater in the manner described above offers the only escape from this embarrassing difficulty.

After the extraction has been progressing about a week and all of the free fat is dissolved, the tissue is removed from the apparatus and run down slowly through the graded alcohols. Owing to the well-known fact that CO_2 is less soluble in a mixture of alcohol and water than it is in either of the two fluids alone, there is always an evolution of gas when they are brought together. It is well, therefore, to make up the graded alcohols sometime before the tissue is placed in them, as the gas bubbles become entangled in the meshwork of the connective tissue and often cause considerable annoyance. After passing through the alcohols the tissues are washed in running water for 24 hours, when they are ready for the digestive mixture. The pancreatin of Parke, Davis & Co. can be used, but for this purpose the preparation manufactured by Grübler after Spaltcholz is better adapted to this use. From comparative tests with weighed amounts of pancreatin and fibrin, it appears that Grübler's pancreatin is more potent and more soluble. The resulting solution, moreover, is almost colorless, which is an important consideration in this technique, as the latter quality of the German pancreatin renders the preparations more transparent while the former naturally makes the digestion quicker and more effective. Only a small quantity of the pancreatin need be used. In general enough to cover the end of an ordinary scalpel handle dissolved in 100 cc. of a 0.5 per cent solution of sodium bicarbonate makes a very effective mixture. Inasmuch as the products of digestion inhibit the action of the enzyme, it is better to use a dilute solution of trypsin and renew it often than to make a stronger mixture and allow it to act over a longer period of time. If the fluid is changed every 48 hours, good results, so far as the digestion is concerned, are assured. To prevent putrefaction it is well to use enough chloroform to cover the bottom of the vessel in which the digestion is made. Thymol accomplishes the same result, but has the disadvantage of staining the tissue a dirty brown, which interferes considerably with the sharpness of the picture obtained under the microscope after the digestion and clearing are complete. During the progress of the digestion, the heat of the thermostat volatilizes the chloroform and the digestion mixture becomes filled with small bubbles of gaseous chloroform, some of which often lodge in the meshwork of the connective tissue and cause the digesting organs to float about in the fluid. To avoid this, a small elevated stand can be made out of thick paper which not only keeps the tissue raised from bottom of the beaker when the débris of digestion collects, but keeps the volatilized chloroform away from the tissue. A porcelain filter plate elevated on bits of glass tubing serves this purpose quite as well as the paper stand.

The fats which are united to protein, of course, can only be extracted after the tissue has been submitted to the action of the digestive fluid so that it is necessary to extract and digest at least twice. Apparently the action of the enzyme is much more effective on some organs than others, for in some cases the digestion may be complete after a double extraction and double digestion, while in others it may be necessary to repeat each process four times before the connective tissue is completely free from cellular matter. Among the organs that digest the quickest are the thyroid, spleen, lymph gland and lung, while the salivary glands and pancreas and adrenal digest with much greater difficulty. The pancreas itself is apparently more resistant to its own ferment than any other organ which we have tried. This, of course, applies to the organ only after it has been fixed and hardened, as no experiments were made on the fresh

pancreas. In slide digestions, however, the enzyme apparently acts with great ease, since, owing to the thin sections, all parts are freely exposed to the action of the digestive ferment. In pieces, however, this distinct resistance to the enzyme is noted, and even after repeated extractions and digestions some débris remains embedded in the connective tissue framework. In considering the effect of the nature of the tissue on the digestion we should note perhaps that the method works equally well on pathological as well as normal tissue. The writer has, for example, digested a tumor of the thyroid which shows perfectly the changes in the framework resulting from the pathological condition in the gland.

One can usually tell from the appearance of the tissue under the microscope when the digestion is complete. As long as any cellular débris can be seen in the meshwork the extractions and digestions must be continued. When, however, nothing but the framework remains, it is thoroughly washed in distilled water and cleared with glycerine. The framework can then be studied with the stereoscopic microscope. A piece of a digested organ forms in this medium a whitish, refractive, translucent block, which preserves exactly the form in which it was originally cut. The capsule and the larger and finer processes of connective tissue stand out distinctly. All of the form relations of the organ are distinctly shown in three dimensions. The units of structure, the course of vessels and ducts, the relations of lobules or follicles are preserved and yet rendered transparent so that they can be followed with ease. Even the basement membranes can be made out as a fine web between the limits of the lobules of glands like the submaxillary, parotid, sublingual or pancreas. It is sometimes necessary, however, to vary the light in order to bring out some of the finer details. But as a regular routine, all preparations should be studied by means of transmitted and reflected light, with both white and black backgrounds. In this way additional details or different aspects of the same structure are brought into view. As an example of the results obtained by this method, the accompanying drawing of a digested preparation of the thyroid is given. One can note the arrangement and shape of the follicles, the course of the larger blood-vessels and their relations to the units of structure. Outlining the follicles the basement membranes

FIG. 1.

can be faintly seen. Detailed observations on the thyroid, salivary glands and pancreas, prepared by this method, will appear in a later paper.

After a study of the framework in three dimensions has been made and careful drawings obtained, it is possible, either on the same or another piece of the organ similarly prepared, to investigate the reticulated tissue up to the highest powers of the microscope according to the original method of Spalteholz. The glycerine is washed out and the tissue embedded in paraffin and cut in sections from 4 μ upwards. Some sections can be stained with iron hæmatoxylin, fuchsin, nigrosin, Mallory's method or in aniline blue alone. Prepared in this way the immersion lens, as was first shown by Spalteholz, gives the finest details of the arrangement of the individual fibres and the smaller fibre bundles. In some way, sections in celloidin give even better results than the thicker sections in paraffin. They can be cut from 15 to 80 μ thick and stained with an 8 per cent solution of acid fuchsin. Prolonged washing in alcohol removes the fuchsin from the celloidin while the fibrils remain deeply stained. These preparations preserve a suggestion of the third dimension and yet the fuchsin stains perfectly, even the single fibrils.

This extension of Spalteholz's original method yields some fruitful results in the study of the framework of organs, because it fills a distinct gap which has hitherto existed in our technique on the connective tissues. It is a tedious method at best, for it is difficult to get good preparations in less than a month; indeed some of the writer's preparations were extracted and digested alternately for nearly three months. For rapid work Mall's frozen-section method will still be of service to us, and the methods of Spalteholz and his pupils will always be required in studying the framework of an organ in order to give us control pictures in ordinary stained preparations.

Explanation of the Figure.

Fig. 1. Framework of the human Gl. thyreoidea from a male about 45 years of age. ×13.

The preparation does not include a portion of the capsule, but is cut from the middle of the gland. The follicles closely packed together are separated from each other by the basement membranes and a slight amount of interfollicular connective tissue. The course of the vessels can be followed into the depths and the shape of the superimposed follicles easily made out.

THE TOXIC EFFECT OF ALCOHOL ON THE GANGLION CELLS OF THE RETINA.[1]

ABSTRACT.

By Harry Friedenwald, M. D., Baltimore.

Ward A. Holden, in 1899, reported that he had given a dog methyl alcohol, had produced amblyopia and on examining the retina by Nissl's method had found sufficient evidence of degeneration in the ganglion cells to lead him to the conclusion that it is this degeneration that produces the amblyopia. Since then Birch Hirschfeld has investigated the effect of methyl alcohol (as well as that of a number of other poisons). He experimented on rabbits and on chickens, and gave sufficiently large doses to produce intoxication. The animals rapidly lost weight and soon died. The retinæ all showed marked signs of degeneration in the ganglion cells, and in one case changes were found in an optic nerve very suggestive of the lesion observed in man in chronic alcohol and tobacco amblyopia. Objection has been raised against accepting these experimental results on animals as necessarily identical with the effect of chronic alcohol poisoning on man, and the differences in the clinical features of acute methyl alcohol and of chronic ethyl alcohol blindness have been pointed out. In order to obviate these objections the writer used various forms of alcohol in smaller doses over an extended period (almost four months). Pure and commercial methyl alcohol, absolute ethyl alcohol and essence of Jamaica ginger made of 95 per cent ethyl alcohol were employed, and the animal selected was the rabbit. The period of experimentation was sufficiently long, as was shown by the high degree of cirrhosis of the liver found in the rabbit fed with absolute ethyl alcohol. The animals were all in apparently good health when killed.

The effects of all four substances were alike. The retinal ganglion cells showed marked degeneration and the inner and outer nuclear layers were less affected. It was evident that methyl and ethyl alcohol act similarly on the retina in chronic poisoning, and that the degenerative changes produced by chronic alcohol poisoning are similar to those found by Holden and by Birch Hirschfeld in acute methyl alcohol poisoning.

These experiments are the first in which ethyl alcohol has been used, as well as the first in which degenerative changes have been demonstrated in chronic alcohol poisoning.

[1] Paper read at Neurological Section Med. and Chir. Faculty of Maryland, Dec. 13, 1901.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

October 7, 1901.

Exhibition of Medical Cases, Primitive Spleno megaly with Anæmia, Cirrhosis of the Liver and Jaundice.—Banti's Disease. DR. OSLER.

We have been much interested of late in cases of enlarged spleens, occurring independently of leukemia, malaria and the chronic, passive congestion, such as occurs in cirrhosis of the liver and diseases of the heart. Our cases may be divided into four groups: 1. Cases of enlarged spleen in otherwise perfectly healthy persons who have no marked anæmia, and who suffer only with the mechanical discomfort of the greatly enlarged organ. 2. Cases with changes in the blood not unlike those of pernicious anæmia. In one instance the enlarged spleen disappeared under treatment but the woman relapsed a year later and died. Several of our cases of enlarged spleen in young children come in this group. 3. Primitive spleno-megaly of long duration—8, 10 or 12 years—with an anæmia of the chlorotic type, a special tendency to hemorrhages, particularly from the stomach, and in some cases with pigmentation of the skin; and 4. A group of cases with anæmia, enlarged spleen, cirrhotic liver and jaundice. This last group of cases was studied by Banti and the condition is sometimes called by his name. The case before you is, I believe, a good illustration of this variety.

The woman is 40 years of age, and came in complaining of swelling of the abdomen and legs with pain in the back. She had suffered the usual infantile and infectious diseases and had pneumonia 8 years ago. Eleven years ago she had malaria for the first time and then for four successive years had chills in spring. The tumor in the abdomen has been present since the first malarial attack. During the first four years it grew but has not increased in size since. When admitted August 3, 1898, the tumor measured 17 cm. and she had ascites. Blood examination then showed hæmoglobin 47 per cent, red cells 2,500,000, leucocytes 2500. When discharged September 30, the hæmoglobin had risen to 50 per cent, the red cells to 3,500,000 and the leucocytes remained about the same. The patient entered the hospital again September 30, of this year, having been fairly well and able to work during the interval. Jaundice had existed for about a month, and for two weeks before admission she had headache and œdema of the feet and legs. On admission there was a moderate ascites. The edge of the liver could be readily felt and was evidently cirrhotic; the spleen extended 18 cm. from the left costal margin and 15.5 in width. The blood examination was interesting when contrasted with that of 2 years ago. The hæmoglobin was 75 per cent, the red cells 5,760,000 and the white cells 4370. She has a few of the papillary angiomata of the eyelids.

That she has cirrhosis of the liver in addition to the chronic enlargement of the spleen is, I think, most probable.

The cases belonging under group 2, discovered accidentally, are apt to be mistaken for ovarian tumors, in fact, in some of the early cases of removal of the spleen in this country this mistake was made.

DISCUSSION.

DR. HUNNER.—It may be of interest to state that we have a case of this kind in the wards now, about ready to go home, upon whom the diagnosis of ovarian cyst was made. She was 29 years of age and the tumor was discovered three years ago after the birth of a child. She had no particular discomfort from it but complained of weakness and indigestion in addition to the presence of this enlargement. On bi-manual examination a large tumor was felt choking the true pelvis. The notch was plainly felt and the upper portion was considered to be another lobule of the cyst, particularly as we often find dermoids lying in this position. At the operation it was found to be an enlarged spleen in the pelvis. Fortunately, Dr. Schenk had looked up the two other cases that have been operated upon in our department and knew that neither had suffered any particular trouble following the loss of the spleen, but were living and in good health, and so we removed this spleen and the patient has done perfectly well.

DR. OSLER.—Were all three of these cases mistaken for ovarian tumors?

DR. HUNNER.—The first was diagnosed as an ovarian cyst, and the second was thought to be a cystic kidney.

Gastrotomy for Removal of False Teeth. DR. FINNEY.

In 1886 Dr. H. Richardson, of Boston, reported the first case of gastrotomy for the removal of a plate of false teeth from the lower portion of the œsophagus. Shortly after, Dr. Bull, of New York, reported the removal of a peach stone from the lower portion of the œsophagus through a similar incision.

In 1892 I reported in the JOHNS HOPKINS HOSPITAL BULLETIN a third case of gastrotomy for the removal of a peach stone from the lower end of the œsophagus, and two years later I operated upon a second case almost identical with the first. These four cases all recovered. Since this time many similar operations have been reported in the literature.

To-night I show a patient upon whom I operated ten days ago for the removal of a plate, containing one false tooth, which had been swallowed during sleep. In this case I performed a preliminary œsophagotomy, thinking it might be possible to remove the plate through the œsophageal wound. This proved impossible, however, because the prongs of the plate, which held it in place, pointed upwards as the plate lay in the œsophagus, and prevented its being withdrawn. I could push it down, but could not withdraw it, as those prongs engaged at once in the mucous membrane. It was lodged about the level of or a little below the cricoid cartilage.

Finding it impossible to withdraw it, I pushed it down as far as I could with a pair of forceps, and then opened the stomach through a median incision. With my hand in the stomach, and a finger through the cardiac orifice, I could just touch the plate, but could not remove it. I then made use of the same procedure used in my preceding cases, namely, passed a bougie from below upwards through the abdominal wound, the wound in the stomach, the cardiac orifice, the œsophagus, and then brought it out of the patient's mouth. To the end of the bougie a strong string was tied, and to this a small sponge was attached. The sponge was then drawn down through the patient's mouth into the œsophagus and thus the œsophagus was thoroughly swept out and the dental plate brought down into the stomach, whence it was readily removed by the fingers. The stomach contained a large amount of undigested food and it was with difficulty that the peritoneal cavity was kept from soiling with stomach contents. The stomach wound, which was about two and one-half inches long, was closed with mattress sutures and the abdomen closed without drainage.

The œsophageal wound was also closed with mattress sutures, and an iodoform gauze drain carried down to the line of sutures and the skin wound left open. There was no leakage from the œsophagus at all and the patient made an uninterrupted recovery. My first peach stone case was complicated by a periesophageal abscess which I subsequently drained through the posterior mediastinum, after resecting a portion of one rib.

Excision of the Gall Bladder. Dr. Finney.

I wish to report to-night four cases of excision of the gall-bladder in which I have made use of a new method of procedure. It differs from other methods in that one reflects from the fundus of the gall-bladder lateral flaps of the peritoneal and muscular coats of the gall-bladder which cover up the raw area left on the under surface of the liver. The steps in the operation are as follows:

The gall-bladder is exposed in the usual way and the peritoneal cavity thoroughly protected by a gauze packing. Parallel incisions are then made beginning at the fundus and extending upwards toward the neck of the gall-bladder. These incisions should be made on either side far enough from the attachment of the gall-bladder to the liver so that when the gall-bladder has been removed these peritoneal flaps may be replaced and thus cover completely the denuded surface of the liver.

The incision should be carried down only through the peritoneal and muscular covering of the gall-bladder, and then with a small, blunt dissector, or the finger, the gall-bladder can be rapidly separated from its attachments to the liver. Toward the neck of the gall-bladder the reflection of peritoneum forms a mesentery-like attachment to the cystic duct. The two peritoneal layers are so close here that they cannot readily be separated, so one divides the fold just as one would divide the mesentery in an intestinal resection. This dissection is carried up to the junction of the cystic and common ducts. Here a peritoneal cuff is reflected just as in an apendicectomy; the cystic duct and artery are ligated close to the common duct, the peritoneal cuff is then inverted over the raw end of the cystic duct, which has been treated in the same way as the stump of an appendix. The free edges of the peritoneal flaps which have been reflected on either side from the fundus and body of the gall-bladder, are then brought together by a few sutures and in this way the raw surface of the liver is completely covered in. The gall-bladder is thus removed intact without opening it and without in any way soiling the peritoneal cavity.

I have made use of a stitch or two taken in the fundus of the gall-bladder, which serve very well as retractors or handles to the gall-bladder during the necessary manipulation.

In my last case the operation was accomplished so quickly and satisfactorily, and the hemorrhage was so insignificant, that I felt justified in closing the abdominal cavity without drainage. This patient has made a most satisfactory recovery.

Of course this operation is best carried out in those cases in which the gall-bladder is distended and its walls thickened. In two of my cases the gall-bladder was very adherent to surrounding structures, but this interfered very little with the operation. In the case of a contracted gall-bladder, the steps of the operation would have to be modified somewhat, that is, in taking one's peritoneal flaps.

The chief advantages of this operation over others are that the gall-bladder is removed unopened and the possibility of infection from this source is thus done away with. The raw surfaces are covered over with peritoneum, thus lessening the danger of adhesion. Drainage is unnecessary.

It would seem as if the analogy drawn by certain writers between the appendix and the gall-bladder was well founded; the function of neither organ is entirely understood; both are fruitful in the production of trouble; both can be dispensed with without any inconvenience on the part of the patient.

The anatomical structure of the appendix and of the cystic duct renders them both amenable to the same treatment, that is, ligation excision and investment of the stump with peritoneal covering. In a subsequent paper upon this subject, we propose discussing at greater length the indications for and advantages of cholecystectomy over other operations upon the gall-bladder.

My four cases have all made rapid and complete recoveries. In the first three I made use of an abdominal drain of iodoform gauze carried down to the stump of the cystic duct; no leakage occurred in any of these cases. In my last case I closed without drainage. In all four cases the gall-bladders were large and distended, containing from one to several hundred gall-stones.

Discussion.

Dr. Halsted.—To close the stump of a cystic duct after cystectomy in such a way that it will not leak during the process of healing is a matter which will surely interest all

surgeons experienced in the surgery of the bile passages. A biliary fistula worries and often weakens a patient, and reminds the surgeon most unpleasantly that the surgery of the bile passages is not a closed chapter. I cannot quite agree with Kehr, who well deserves to be recorded as an authority in this branch of surgery, that a biliary fistula after ectomy is of so little consequence. Nor do I believe that the drainage of the stump of the cysticus with the expectation of a fistula is an ideal surgical procedure. Furthermore, from our comparatively small experience, I should not suppose that it would be necessary to drain a ductus hepaticus in about 37 per cent of all operations for gall stones.[1]

So the temptation to close the cystic duct in certain cases is irresistible. Last spring, with this object in view, I made a cuff from the outer coats of the cystic duct, but the cuff was too short to satisfactorily effect a solid closure of the ligated and sutured duct. It was my intention to make this cuff long enough at the next cystectomy. In the meantime Dr. Finney has carried this plan to its limit and has enucleated the gall-bladder, as well as the cystic duct. So successful was he that in one of the two cases, which he has to-night reported, he confidently closed the abdomen without drainage. Kehr would as confidently predict a second operation for a certain portion of cases so treated, and last year he still urgently recommended drainage, not only of the wound, but also of the bile passages. Mayo Robson, in his book "Diseases of the Gall-Bladder and Bile Ducts," describes a procedure which probably embraces mine and Dr. Finney's also. He speaks of stripping the *peritoneum* from the top and back of the gall-bladder and from the entire circumference of the cystic duct, and utilizing this coat to cover the stump of the cystic duct in cases of excision of the gall-bladder. As he could hardly make a flap of peritoneum only, it is likely that he would do what Dr. Finney did in the two cases reported to-night. It is possible that William J. Mayo, in excising the mucous membrane of the gall-bladder, would take about the same route between the coats. The thickness of the peritoneo-fibro-muscular flap would vary considerably.[2]

Some sure and simpler method must be devised for determining positively the presence of stones in the ductus choledochus after excision of the gall-bladder.

Exhibition of Surgical Cases. DR. FOLLIS.

CASE 1.—This patient, aged 11, was shot in the abdomen with a 22-calibre revolver 2½ hours before admission. He had taken a full meal five hours before the accident. On admission his temperature was 99.4°; pulse 114; leucocytes 35,000. The wound of entrance was at the left of the umbilicus and about at the middle of the left rectus muscle. He was operated upon three hours and fifty minutes after the injury, the incision being made in the course of the bullet. Considerable bloody fluid was found in the peritoneum. There were three small perforations in the jejunum and the bullet had gone through the mesocolon and lodged somewhere posteriorly. The three perforations were sutured, the general peritoneal cavity was wiped out, and a piece of iodoform gauze was left at the point from which some hæmorrhage seemed to arise. The bullet was not found. He was very much shocked, and after the operation the pulse reached 160. For the first five or six days he was in a precarious condition. He was given infusions, stimulating enemata, and strychnia. Nothing was given by mouth until after the bowels had moved spontaneously, on the fifth day. Only liquids were given until the tenth day, when soft diet was allowed. He made a very good recovery. Only three perforations were found at operation, but there was probably a fourth, which took care of itself. An X-ray photograph taken after the operation showed the bullet embedded in the psoas region.

CASE 2.—This patient, a German, aged 71 years, was admitted on September 1, with a strangulated right-sided inguinal hernia, which had never previously been strangulated. Strangulation had occurred twelve hours before entrance.

The general condition of the patient was good; pulse 70; temperature 100°; leucocytes 14,000. While preparations were being made for operating, his feet were elevated and an ice bag applied over the tumor. Two doses of morphia were given, as a preliminary step to cocaine anæsthesia. Under local anæsthesia, cocaine 1-1000, an incision was made in the right inguinal region. The aponeurosis of the external oblique was divided, and the ileo-inguinal nerve was found, cocainized, and divided. A large mass of indurated omentum was found in the sac, together with a loop of gangrenous small intestine 24. cm. in length. The constriction was relieved, and the loop of strangulated bowel with seven or eight cm. of good intestine on each side was brought out and left on the abdominal wall. Gauze was packed loosely about this. This was done to see whether the bowel would clear up, as had happened in two cases of Dr. Mitchell's, in which the bowel seemed in bad condition at the time of operation, but which after twenty-four hours he was able to replace. After twenty-four hours the bowel appeared green, and a resection was done and an end-to-end anastomosis made, using Dr. Halsted's rubber bag. This procedure was carried out entirely outside the general peritoneal cavity, which was walled off by gauze and 24-hour adhesions. The field of operation was then cleaned and the bowel was replaced in the cavity, and a small gauze drain inserted to point of suture. This second operation was done entirely without anæsthesia, with the exception of two ⅛ gr. doses of morphia, one given an hour before, and one at the beginning of the

[1] "Of 84 laparotomies for gall-stones there were 28 simple ectomies and 31 combined with drainage of the hepatic duct."—Kehr, Verhun. d. Deutsch. Ges. F. Chirurg., 1900, pp. 172.

[2] In a case recently operated upon by me, it was so difficult to enucleate the gall-bladder that I twice entered it, before and behind on the same parallel, but could easily strip a flap from the cystic duct; with this I effected a satisfactory closure, but I thought it safer to drain down to the stump.

operation. The excision and suture were entirely painless; but when the parietal peritoneum was manipulated in replacing the bowel, the patient complained of pain. An uneventful recovery followed.

Since the opening of the hospital, eleven cases of strangulated hernia with gangrene of the bowel have been admitted. In four of these an immediate end-to-end suture was done. One of these patients recovered. Four other cases were treated by excision of the gangrenous portion of the bowel and the formation of an artificial anus, with the idea of doing a secondary suture later. Two of these died before the second operation; the other two died after the anastomosis had been made. In one case, the strangulated loop was thought to be viable and was returned to the peritoneal cavity, but evidently it was not and the patient died of peritonitis. One case of Dr. Bloodgood's was treated like the present one, except that the bowel was sutured to the parietal peritoneum and the general cavity was opened at the second operation before the suture was done. This patient had a general anæsthetic at the second operation, and died of broncho-pneumonia.

Discussion.

Dr. Finney.—I would like to report in this connection an interesting case which is as yet unreported. I was called about three years ago to see an old lady with a femoral hernia which had been strangulated for four days. Her condition was very weak and precarious at the time. I cut down upon the hernia and found a loop of intestine, strangulated, black, and beginning to be gangrenous. Her condition was such that I simply pulled the intestine out into the wound after having relieved the constriction, packed it about by gauze and left it. During the following night she was very restless and vomited violently, due, apparently, to the ether.

During her straining she forced out two or three feet of small intestine into the dressing. This was replaced the next day by Dr. Bloodgood, in my absence, and he then made an opening into the gangrenous loop; this was followed by immediate relief of her distention. I had not opened the loop at the time for fear of soiling the peritoneal cavity, intending to wait until protective adhesions had been formed.

The patient from this time made an uninterrupted recovery, except after we began to feed her by the mouth, it was noticed that in a short while quantities of partly digested food poured out of the abdominal fistula and she began to lose weight rapidly.

Dr. Pancoast, the resident surgeon of the Union Protestant Infirmary, of which institution the patient was an inmate, overcame this loss of intestinal contents by a very ingenious procedure. He inserted a rectal tube into the lower opening of the bowel and with a funnel inserted into the upper end of the rectal tube, he, by placing the patient upon her side, caught the intestinal contents as it poured out of the upper opening in the bowel. In this way he bridged over the break in the continuity of the intestinal canal with very little loss of intestinal contents.

The patient at once began to pick up in weight and strength, and after two or three weeks, became quite strong and robust again. I then cut down upon the fistula, and found that the strangulated loop of bowel had occurred in the very uppermost portion of the jejunum, which explained the patient's sudden loss of weight.

I did an end-to-end anastomosis with the aid of Dr. Halsted's rubber bags, and the patient made an uninterrupted recovery, and is now alive and well some three years after the operation.

A Case of Labor in a Bicornate Uterus. Dr. Bettmann.

Mrs. R. W., aged 35, without any history of apparent deformities in any member of her family, had given birth to eight children at term and had miscarried once. Three of her labors had been by the occiput and four by the breech, the last two children being born dead.

Present pregnancy.—Normal except for some hemorrhage throughout the last week. Pelvis normal.

Labor.—Seen for the first time by the Out-Patient Department twelve hours after onset. L. S. T. T. Frank breech. What was thought to be a marked cystocele protruded from the anterior wall of the vagina. Cervix was half dilated, soft and non-resistant. The breech was just entering the superior strait. The heart during the time we were in attendance (four hours, circa) had been well heard to the left of the umbilicus, when suddenly it was discovered to be inaudible. Internal examination showed that the breech had rotated into a posterior position, so that the sacrum lay directly parallel to the sacrum of the mother. The cord of the child was palpated and was found to be pulseless. Extraction was undertaken in the interests of the child, which was delivered within ten minutes but could not be resuscitated. In the manipulation, consisting of alternate traction in each, given by means of the index finger, a partial vaginal septum about 3 cm. in breadth was discovered in the middle third of the vagina, running from the anterior to the posterior wall directly in the mid-line. The probable diagnosis of double anomaly of the uterus was made, thus accounting for the persistence of breech presentation and the abnormal rotation of this breech. The child was a male weighing seven pounds, and showed at autopsy only the signs of intrauterine asphyxia. The patient died 36 hours after labor. She had apparently been doing perfectly well up to within an hour before death, the only anomaly in the puerperium being retention of urine and a small external hemorrhage eighteen hours before death.

The *autopsy* revealed a uterus bicornis unicollis, with rupture through the lower uterine segment of the left (pregnant) cornu, extending a slight distance into the vagina. The rupture did not extend above the contraction ring (which was well marked), so that the extravasation of blood resulting therefrom was subperitoneal and not intraperitoneal. All of the pelvic connective tissue of the left side was infiltrated with clotted blood, which also extended across the

median line and up the rectum as high as the sigmoid flexure. All the other organs were normal.

Dr. Bettmann then discussed the various types of double anomalies of the uterus, illustrating these by means of diagrammatic charts. He spoke of the embryological and obstetrical significance of the various types and explained the rupture of the uterus in his case in the following manner:

The axis of the pregnant cornu deviated 45° from the axis of the pelvis, so that traction made in the axis of the pelvis exerted force directly against the lower uterine segment instead of along the axis of the uterus. The position of the tear upholds this theory, for it is in the left side of the lower uterine segment (the left cornu being the pregnant one). At the time extraction was undertaken the presenting breech had not yet cleared the cervical rim, so that traction upon it pulled it directly against the lower uterine segment.

October 21, 1901.

Dr. William Osler was elected President of the Society for the ensuing year and Dr. Hunner was re-elected Secretary.

Exhibition of Medical Cases, Post-Typhoid Insanity. DR. MCCRAE.

This case is of considerable interest on account of the rarity of the condition, namely, marked mental symptoms following typhoid fever. Since some of you saw him in the clinic last week he is convalescing from the fever but he is still showing marked mental features. Briefly the history is that the patient was admitted on the 14th of September with fairly severe symptoms of typhoid. He ran an ordinary course as far as the fever goes and is now at the end of the sixth week. Early in the disease he showed marked mental symptoms, being delirious and later suffering from delusions. This was followed by a period of melancholia, but within the last 48 hours he has again shown a change, and this time for the better, so that it looks now as if he would soon be well.

Various classifications have been made of the insanities following typhoid fever. I should find difficulty in putting this case under any of those definite headings. The prognosis is exceedingly good, for there is every chance that his mental condition will clear up entirely.

Adherent Pericardium.

This case is shown not so much on account of the special features of the case but rather as the type of a condition of interest to us clinically. The reproach has often been made that the pathologist makes many of our diagnoses for us, and possibly first on the list of such conditions is that of adherent pericardium.

This boy has a rather puzzling heart. He is 19 years of age and came in complaining of shortness of breath. In April of this year he was in a hospital at Harrisburg with what he thinks was rheumatism, but states that he had attacks of shortness of breath prior to that time. He has been here now since September 27 and has made very little progress. On inspection we find some precardial bulging which suggests that the illness has been of longer duration than the history would lead one to suspect. The heart is slightly enlarged and there are some indefinite and variable murmurs. He has none of the classical symptoms of adherent pericardium, but a striking thing to my mind is that he has not improved under treatment and that he has a slight systolic retraction, about the third or fourth interspace, with no retraction behind and no fixation of dulness.

In this connection I want to show a specimen from a patient that has been in the ward within the last few days, and in this case we had been able to follow the history from the onset, so far as the heart symptoms were concerned. The man was 56 years of age and admitted in January of this year for a sudden attack of acute pericarditis, which was regarded as idiopathic, and at the end of two weeks he was discharged apparently well. He was readmitted in April with a history that was significant. Two days previously he had an attack of shortness of breath with sudden pain and dyspnœa. The heart was slightly enlarged. Within a few weeks he was again discharged, apparently well, but in June he returned for another brief stay and in September he returned and remained until his death. We thought the man had adherent pericardium from the attack of pericarditis, the acute onset of the myocarditis and the subsequent history. The specimen here shows a generally adherent pericardium.

Now briefly to speak of one or two points in pericarditis. First, we must bear in mind that pericarditis means often an involvement of the myocardium and even of the endocardium. A man who runs the whole course of his myocarditis in 6 months may be spoken of, I think, as an acute case. In this specimen there was a well-marked myocarditis as well as a pericarditis. Such a case as the patient had shown will rarely be diagnosed from the physical signs. Any one looking at this boy for the first time, say a week ago, would probably not make the diagnosis. It impresses me, however, much the same way as the other case I have referred to which we were able to follow throughout the whole course. The symptoms are out of proportion to any discoverable lesion, and he shows no signs of improvement.

DISCUSSION.

DR. HURD.—It is evident that in the case shown of post-typhoid delirium the patient has suffered from a prolonged exhausting disease and the condition of apparent depression following such exhaustion is not unusual. The mental faculties were evidently temporarily exhausted from the delirium but the state of the patient is not one of acute distress, such as is characteristic of true melancholia. In some cases the mental aberration of a typhoid fever patient is not recognized. In two instances that have come to my knowledge, patients who had given no evidences of mental aberration during the attack of typhoid fever made and signed their

wills. Two or three months after when fully convalescent both were much astonished to learn that wills had been executed. Unquestionably the mental state of these persons must have been an unnatural one at the time the wills were made, yet it did not attract the attention of friends and bystanders or the lawyers who drew the wills.

Exhibition of Pathological Specimens. DR. MACCALLUM.

The patient, a boy, entered the hospital in September, having passed through an indefinite illness in the Charity Hospital in New Orleans during the preceding winter. He was deeply jaundiced, passed very little urine, and that deeply bilestained and containing besides albumen and casts, leucin and tyrosin. After several days of delirium he died.

At the autopsy there was marked ascites and the abdominal organs were very much congested. The liver, however, showed the most extensive changes. It was very small, tough and flabby. From the dorsal surface of the right lobe there projected a large dark green nodular mass, and similar but smaller masses could be seen on the under surface. On a section through the whole liver these stood out sharply from the remaining substance; they had a general lobular arrangement, differing from that of a normal liver in the great size and irregularity of the lobules. The remaining liver substance was grey brown in color, showed very indefinite lobulation and resembled that seen in the condition of senile atrophy.

Microscopically the nodules appeared to be the most nearly normal of the tissues found in the liver. They appeared like greatly enlarged liver lobules in which the radiate order of the liver cells is much disarranged, and often the relations of central and peripheral blood-vessels were not to be made out. The cells in these masses were often very atypical in appearance. The remaining liver substance showed roughly the ordinary lobulated appearance, but the liver cells were practically lacking, the radiate appearance of the lobule being maintained by the arrangement of the capillaries and the greatly thickened intervening connective tissue. In the periphery great numbers of newly-formed gall-ducts were visible branching from the interlobular gall-ducts to push into the lobule toward its centre. These often anastomosed toward the centre and the cells there had taken on to a certain extent the appearance of liver cells.

As it is known that in acute yellow atrophy the destruction of cells is marked on the periphery of the lobule, it seems probable that these must be considered as entirely new formed from the interlobular gall-ducts. The case corresponds almost exactly with those described by Marchand and Stroebe, who explain the condition as the result of acute yellow atrophy, recovery from which is associated with attempts at regeneration on the part of the liver, this regeneration being carried out either by the formation of large nodules from portions of the liver which have escaped destruction or by a diffuse proliferation of the bile-ducts, whose cells may reform liver cells and take on their functions.

The Importance of the Adducted Position in the Normal and Weakened Foot. DR. SAMPSON.

(See January BULLETIN, 1902, page 8.)

DISCUSSION.

DR. HURD.--Those who have not followed Dr. Sampson's work will be interested to know that by means of shoes made upon the lasts devised by him a number of physicians of the Hospital who suffered from flat foot, because of constant standing in the operating rooms, have found themselves greatly relieved.

Pathological Report of a Fatal Case of Enteritis with Anæmia Caused by Uncinaria Duodenalis. DR. YATES.

(See December BULLETIN, 1901, page 366.)

November 4, 1901.

The meeting was called to order by Dr. Hurd.

Indurated Scrofulous Erythema, Exhibition of Case. DR. GILCHRIST.

This patient presents an eruption on the skin which forms one of a very interesting group of diseases. It is a rare form of skin disease and I think is the only case we have seen in the dispensary. The patient is a young girl of 19 years who applied for treatment, on the first occasion, about 20 months ago, when she showed on the left leg a chronic lesion which on a cursory examination looked like a syphilitic patch. The lesion measured 5 by 6 cm. and was of a dull reddish color, very much indurated, and presented two or three punched out ulcers with undermined edges. There was a family history of tuberculosis but none in the patient though she was anæmic and much run down. A guinea-pig was inoculated with scrapings from the largest ulcer and the animal died within 24 hours, but not of tuberculosis. The patient got well under treatment by the use of iodoform applied locally and Blaud's pills given internally. She now reappears with similar new lesions on the right leg, one patch being almost an exact reproduction of the first lesion. A portion of this ulcer has been curetted and guinea-pigs inoculated subcutaneously; the animals are still living. One small ulcer was excised and the sections from the tissue did not show any tuberculous structure, nor were any bacilli found.

There is a group of diseases of the skin, such as lupus vulgaris and tuberculosis cutis, which can be definitely determined to be tuberculosis of the skin. There is also the warty form of tuberculosis which occurs on the knuckles usually from inoculation. Then there is a second group of diseases mentioned under a variety of names with the history of tuberculosis in the family but where only recently have tubercle bacilli been discovered in the local lesions. One of this group is *Erythema Induré Scofuleux*, of which this case is a typical example. Quite recently McLeod, of London.

has demonstrated the presence of tubercle bacilli in the tissues, which fact places this disease in the first group. This group also contains the scrofulous gumma with broken down glands, lichen scrofulosorum, acne varioloformis, scrofuloderma and the necrotic granuloma, a form which has been described under many names, but it seems to me the nomenclature might be very much simplified if they were all grouped under the one heading of tuberculosis of the skin and given different names according to the clinical pictures, just as we do in the case of ring-worm where the parasite is practically the same but the name differs according to the location of the lesion.

A Case of Æstivo-Autumnal Fever with Unusually Few Parasites in the Peripheral Circulation. DR. THAYER.

The patient that I wish to show you this evening is a young woman, 18 years of age, who was admitted to the hospital on the 8th of September. There are no facts of importance in her family or personal history excepting that in the spring and fall of 1900 she suffered from chills and fever. Five days before entrance she began to complain of general malaise and on the following day had a chill. This was repeated on the succeeding day, and two days later she took to bed. On entrance the physical examination showed little of importance; the temperature was 100.7°; the thorax and abdomen showed nothing remarkable; the spleen was not palpable; there was some hypogastric tenderness, due probably to a distended bladder. The colorless corpuscles were reduced in number. No malarial parasites were found after several examinations.

The temperature fell gradually, reaching a normal point on the 12th of September, four days after entrance to the hospital, and remained normal during five days. On the 17th it touched 99°. On the 19th it rose again to a point a little above 99°, and on the evening of the 21st it was a little above 100°. On the 22nd there was a chill followed by fever. The temperature remained elevated somewhat over twelve hours, just how long it is impossible to say as it was not recorded with sufficient frequency. At 8 A. M. on the 22nd it was normal, but in the evening it rose again to 101.3°, reaching the normal point on the morning of the 23rd. Again on the 23rd there was a febrile paroxysm, the temperature reaching 103° and falling gradually to a subnormal point on the evening of the following day. During this time the patient complained much of headache and of abdominal pains localized for the most part in the region of the bladder. There was retention of urine, necessitating catheterization. Repeated examinations of the blood failed to show malarial parasites. Several counts of the leucocytes were made, showing always a subnormal number. Over the right clavicle there was slight dulness; the expiration was somewhat prolonged, and on several occasions a few fine moist râles were heard. Later there was tenderness in the region of the spleen. From the 26th to the 30th there was slight, rather irregular fever ranging between 98.5° and 101.5°. On the 2nd of October the temperature rose to 103.2°, and on the following day it again touched a point about 103°, varying during the next week between normal and 103°. The fever continued, the temperature occasionally remitting but never falling below 98.5° until the 14th of October.

During this period the blood had been repeatedly examined without result, but on the 14th a moderate number of crescentic and ovoid æstivo-autumnal parasites were found. Hyaline bodies were found on the following day. Treatment by quinine was started immediately—0.325 (gr. V) every four hours. The temperature fell to the normal point on the following day and has remained normal or subnormal ever since. The spleen, which at first was impalpable, was just to be felt in the latter part of her illness and was distinctly tender on palpation.

No hyaline forms were noted after the 15th of October, though two ovoid pigmented bodies—gametocytes—were found on careful search on the 4th of November, two days before discharge.

There are several points in connection with this case to which I should like to direct your attention. (1) The irregular and continuous fever. Such charts, due solely to malarial infection, are not common in these regions; yet they are occasionally met with and the explanation is not difficult.

The remarkable periodicity of the febrile manifestations, one of the most striking symptoms of malaria is, as is well known, especially marked in tertian and quartan infections, where the paroxysms occur with almost clock-like regularity.

The cause of this periodicity is intimately associated with the life history of the parasites. The tertian and quartan organisms exist in the blood in great groups, all the members of which pass through their life cycle in unison, the sporulation of all the parasites in such a group occurring within relatively few hours, and the paroxysms have been shown to be definitely connected with the sporulation of these groups of parasites. Every now and then, however, one finds, even in tertian and quartan infections, the presence of a multiplicity of groups, or a tendency toward lack of the definite arrangement of the parasites in groups which, as one might expect, results in the occurrence of more or less irregular or continuous fever. This, however, is very unusual in tertian and quartan infections.

But in æstivo-autumnal fever the state of affairs is different. The majority of cases of æstivo-autumnal fever in this climate show well defined and fairly regularly intermittent fever with chills. In many cases, however, the fever if untreated tends to become continuous or irregular. This is probably due chiefly to the development of a multiplicity of groups of parasites or to the spreading out of the period of sporulation of the existing groups, so as to unduly prolong the paroxysms until they overlap one another. In æstivo-autumnal fever, as has been repeatedly observed, the characteristic stages of the paroxysm are often absent—"dumb chills."

It has also repeatedly been shown that insufficient treatment with quinine tends to disturb materially the regularity

of the fever. It is not impossible that this depends upon an interference with the development of some of those parasites which are not actually destroyed, which results in a disturbance of the regular arrangement in groups.

(2) The second point to which I would call your attention is the remarkable scarcity of parasites in the peripheral circulation. There was considerable question as to the nature of this case. The suspicious signs at the right apex, as well as the nature of the chart, suggested that the fever might be due to an incipient tuberculosis. Typhoid fever was thought of but was not considered probable.

Could such a fever be due entirely to malaria without the discovery of the parasites in the blood on reasonably careful examinations? How are we to account for the gradual disappearance of fever after entrance?

A very interesting fact has been developed on close questioning of the patient, namely, that after the first chill she took two doses of quinine of uncertain amount. This, together with the favorable conditions, rest in bed, and general treatment in a hospital, doubtless accounted for the temporary disappearance of fever, and also, in part, for the absence of parasites on entrance to the hospital. The reduction in the number of leucocytes, the clearing up of the suspicious signs at the apex, and the absence at all times of expectoration, rendered the diagnosis of tuberculosis improbable. There was little, on careful observation of the case, to suggest typhoid fever, and the absence of Widal reaction even at this late period speaks against it. These facts, in connection with the specific effect of quinine, leave little doubt that the case was, from beginning to end, due to malarial infection. The great infrequency of the parasites in the peripheral circulation is an extremely rare occurrence, but it is well to recognize the fact that it is a condition occasionally met with. In quartan fever the parasites are found at all stages of their development in the peripheral blood as well as in the spleen and internal organs. In tertian infections the state of things is a little different, in that the parasites are found during the latter stages of development with much greater frequency in the blood of the spleen than in the peripheral circulation. In the majority of instances of æstivo-autumnal fever this tendency is more marked, in that only young forms are found in the peripheral circulation, and often in cases where the parasites are fairly well arranged in groups, few, if any, organisms are to be found in the peripheral circulation during the paroxysm. But there are cases, like that before us, in which almost the entire cycle of development of the parasites takes place in the internal organs, where examination of the peripheral blood, at whatever period it may be made, reveals but very little. The same condition may be seen—with great rarity, however—in tertian infections. Happily, those instances of æstivo-autumnal fever in which the parasites are not to be found in the peripheral circulation, are rarely cases of great severity. In the great majority of cases of pernicious fever the parasites are numerous in the circulating blood; and, even in æstivo-autumnal fever, the number of parasites in the peripheral circulation is generally a fair index of the severity of the infection. But this does not always hold. I have recently seen a case of pernicious malaria where death occurred during my visit, in which the number of parasites in the peripheral circulation was moderate—a parasite perhaps in every tenth field. There was, however, a moderate number of characteristic macrophages, containing large masses of pigment, cells rarely seen excepting in very severe infections.

In all cases of doubt it is wise not to rely entirely upon examinations of the fresh blood. While examination of the fresh specimen is usually the most satisfactory method of studying the blood, it must be acknowledged that the small hyaline forms of the malarial parasites are only to be recognized by an individual who is thoroughly familiar with the examination of fresh blood in normal and pathological conditions. The unskilled observer is sure to be confused by the vacuolization and decolorization of the red corpuscles so common, particularly in certain febrile and anæmic conditions. In such cases it is better to resort to dried specimens stained by Romanovsky's method.[3] Any one who has studied fresh

[3] In connection with these remarks it may be well to quote Lazear's (Johns Hopkins Hospital Reports, 1901, Vol. X, 1), description of his method of preparing Nocht's modification of Romanovsky's stain. The eosin, which gives the best results is that from the Höchts factory, either A. G. or B. A. If prepared by the following method all good methylene blues give satisfactory results. "Polychrome methylene blue is carefully neutralized. This is done by first adding dilute acetic acid until the solution is acid. When litmus paper is dipped into the solution, it is colored by the methylene blue, but on the margin of the moist portion the acidity causes a red line to appear. The solution is now brought back to the neutral point by the addition of more polychrome methylene blue until the red line fails to appear on the blue litmus paper. The polychrome methylene blue may be obtained already prepared. It can, however, be readily made by heating for several hours, on a water-bath, a solution consisting of—

Methylene blue	1 part.
Caustic soda	1 part.
Water (distilled)	100 parts

After cooling, the solution is to be filtered.

To this polychrome methylene blue an equal quantity of distilled water is added, and then, a saturated solution of ordinary methylene blue, until the red color is completely lost, the solution appearing simply blue. For this purpose about one part of the saturated aqueous solution to ten parts of the diluted polychrome solution will be used.

A solution of eosin is now prepared, according to Nocht, by adding three or four drops of a one per cent aqueous solution of eosin to one or two cc. of water. This is practically a 0.2 per cent solution; it can be made up in quantity. To three or four cc. of the eosin solution, Nocht adds the methylene blue solution until the red color disappears. At this point a fine precipitate is thrown down, and a scum begins to form on the surface.

I found it more satisfactory to keep the two solutions in burettes, as is done by Bastianelli and Bignami. The solutions may be made in large quantity, and the proper proportions in which they should be mixed may be determined once for all

specimens and later examined dried cover-glass smears prepared by this method, will acknowledge that the stained parasites are much more readily picked out than the delicate hyaline bodies in the fresh blood. It is probable that, in a case like that before us, an occasional parasite would have been demonstrable by this method.

(3) An important point in connection with this case is the striking proof afforded by the chart of the therapeutic value of quinine. Few things are more impressive than the instantaneous and specific effect of quinine as observed in a case of this nature. And in connection with such a chart it is perhaps fitting to emphasize again the fact that quinine is a true specific—that wherever one may meet with a case of continued fever, no matter in what part of the world, if the vigorous use of quinine be followed by no definite break in the temperature curve, *the case is not malarial.* It has been definitely proved that continued fevers which resist quinine are due to other causes. The diagnoses of "Simple continued fever" and of "Typho-malarial fever," which were once so common in this very town, and are still, alas, only too frequent in certain parts of our country, all melt away before accurate laboratory methods, and resolve themselves generally into plain typhoid fever.

DISCUSSION.

DR. MCCRAE.—It is very often a debated question when one has overlooked a condition whether one prefers not to have considered the possibility of it or prefers to remember that it was considered and discarded. The way the temperature fell after admission made us think it was one of febricula. With the onset of sudden chill and fever we at once thought of malaria and felt no doubt that we had overlooked that cause at first but repeated examinations of the blood were negative. The patient had definite signs at one apex, there was the continued fever with repeated sweats and she was going down hill very rapidly, so that I personally thought the case one of tuberculosis, although no tubercle bacilli could be found. It is a reproach often brought against the profession south of Mason and Dixon's line, that in tuberculosis time is often lost by treatment for malaria, and I suppose it is only fair that we should now have a chance to check up a case on the other side. I did think very decidedly that the case was one of tuberculosis of the lungs with secondary involvement of the peritoneum as the cause of the abdominal pain.

DR. HURD.—I think it unwise to make a diagnosis of febricula in the light of an experience of a physician who had the care of a patient at a summer resort in Canada with a moderate temperature for 10 days. He feared typhoid fever, but as the temperature only lasted 10 days and the patient seemed to get well he thought he had to do with a febricula. He repeated the Widal test from time to time and eventually, after 40 days, the reaction was secured showing that the case had been one of typhoid after all.

Nervous Manifestations of Pernicious Anæmia. DR. MCCRAE.

Out of 50 cases of pernicious anæmia in the hospital about 20 have shown nervous manifestations of one kind or another. I have gone over the cases with the view of classifying the nervous symptoms but without determining any definite groups. We have at one end of the series the merely sensory disturbances and at the other end complete paraplegia with loss of control of bladder and rectum. The three cases to be presented are examples of different types.

CASE 1. The first patient is a woman, aged 38, who has probably had anæmia for less than a year. She is an example of the minor manifestations of nervous symptoms, merely numbness and tingling. Her blood on admission showed 1,500,000 red cells and they have now risen to 2,500,000.

CASE 2. A very robust looking individual, but you probably noticed as he walked up that his gait is somewhat shuffling. He complains of pain about the hands and feet and a curious feeling of the hand, being very thick and constantly numb. The reflexes are rather exaggerated, his blood count now is almost normal with hemoglobin of 70 per cent. His condition is one of sensory disturbance with marked spastic condition.

CASE 3. This patient complained at the onset only of some tingling with pain in the legs and weakness. His reflexes were gone; he had difficulty in walking, and there was fairly persistent tingling with pain.

Now you see these three cases show different features and that is fairly characteristic of all our series. I think the

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by a few experiments. The methylene-blue solution varies a great deal in the amount of the unknown nucleus-staining material which it may contain. One solution may require three parts of the eosin solution to each part of the methylene blue, while another, made in the same manner, may require only one part of the eosin solution to three parts of the methylene blue. When the proper proportion is once determined for a given solution, it remains constant.

The eosin and methylene blue solutions should be mixed immediately before use, and the mixture used only once. When kept a day or two, such a mixture may sometimes give the chromatin stain, but always feebly.

Nocht fixed the blood-smears by placing them in equal parts of absolute alcohol and ether, but I obtained my best results by treating with a one-fourth per cent solution of formalin in 95 per cent alcohol, for one or two minutes. The formalin may be kept in 10 per cent aqueous solution, four or five drops of this being added to 10 cc. of 95 per cent alcohol, just before using.

Before placing the specimen in the staining solution, the scum should be carefully removed by means of filter paper. It is best to use a staining-dish with concave bottom, placing the cover-slip on the bottom with the preparation side down. The specimen is left in the stain for from three to twenty-four hours. The scum should be carefully removed before taking out the cover-glass, as it tends to adhere to the specimen if it comes in contact with it, making the examination difficult or impossible."

The hyaline forms of the parasite appear as delicate blue rings. The central part of the parasite is occupied by a large colorless nucleus, at one side of which is a small spot of chromatin substance which takes a deep carmine violet stain.

predominating type has been that of the second case; a spastic condition with marked sensory disturbance. One may regard these nervous manifestations clinically under three headings. First, there are cases that during life show no symptoms but changes are found in the cord post mortem. Most of the cases where the blood count has gone very low show these cord changes. In the second group the nervous manifestations are secondary, as in the two first cases you saw and probably in the third. The third group are those in which the nervous manifestations come on first and the anæmia follows secondarily. I have felt that possibly in regard to the last that they are instances in which the blood condition had not been recognized in the early stage. A fourth group might be added in which certain nervous conditions appear primarily and associated not with primary anæmia but with secondary anæmia. We have seen no case of the kind here.

To speak briefly regarding the pathologic findings in these cases, they practically all show involvement of the posterior column and a few show also involvement of the lateral columns as well. The cervical region curiously enough usually suffers more than others, and as one goes down the cord the process is less marked. Since improvement occurs in the nervous symptoms as the blood improves, I am inclined to think that the anæmia is at the bottom of the cord changes and not that the two conditions are due to the same cause.

Exhibition of Patient and Report of a Case. Dr. Hunner.

The patient before you is a Bohemian woman, 63 years old. She entered the hospital 28 days ago with a very large cystic feeling abdominal tumor, which we diagnosed as an ovarian cyst. She had noticed the tumor five months but had suffered no symptoms until the past five weeks, during which time there had been considerable abdominal pain on the left side. Two weeks before admission she vomited during a severe attack of pain. Having made a diagnosis of an ovarian cyst with probable malignant degeneration, we made a large incision, extending from a point four centimeters above the umbilicus to the symphysis, intending to remove the tumor without evacuation of its contents. On exposure the tumor was found to be covered by a thin veil of omentum; and hanging from its lower border was an omentum of about normal size, with many rounded and ovoid nodules along its distal edge resembling glandular metastases. We at once decided that unless the tumor could be easily removed we would give up the operation. To determine this point the tumor was rolled out of the cavity when it was seen to arise from the region of the transverse colon and to have no pelvic attachments. The transverse colon was closely attached across the under surface of the tumor and it could not be determined whether this tumor arose from the bowel wall, the mesocolon, or the omentum. The splenic end of the transverse colon dipped directly posteriorly from the tumor and was firmly fixed to the posterior abdominal wall. The hepatic flexure, however, was freely movable and gave promise of being easily carried across the cavity to meet the splenic end. No glandular enlargements could be detected in the mesocolon or above.

Enucleation was begun by separating the tumor from the stomach, the bridge of omentum connecting the two bodies requiring about a dozen catgut sutures for its many large vessels. The portions of omentum springing from the hepatic and splenic flexures and meeting the tumor on its sides were next tied off and cut. This left only the vessels of the transverse mesocolon to be dealt with. By raising the tumor and allowing light transmission one could easily determine the circulation of the bowel and the best points for resection on either side of the tumor. Heavy artery clamps were placed on the tumor side of the points for resection, the mesenteric circulation was ligated, and, after placing presection sutures, the bowel was severed at both hepatic and splenic regions, and the tumor with the attached transverse colon removed. An end-to-end suture without the use of mechanical appliances presented no difficulties except for the very short fixed splenic end.

A Mitchell-Hunner mesenteric suture was placed, and then the two sides of the anastomosis were successively built up by first bringing the mucosa coat end to end with a fine catgut whipped suture, and immediately over each of these sutures the other coats were approximated by a mattress suture of fine silk. A row of intermediate mattress sutures of silk finished the anastomosis in a secure manner. A running catgut suture closed the A-shaped space in the transverse mesocolon. A small gauze wick was introduced through the upper end of the abdominal wound and carried down to the site of anastomosis. The entire operation from incision to closure occupied two hours and fifteen minutes. The patient had lost practically no blood and left the table with a pulse of 96.

She made a rapid recovery without special event until the twenty-first day, when, after walking about the ward, she complained of pain and tenderness in the popliteal space of the right leg. Fearing phlebitis we kept her in bed with the leg elevated for the next two days, when all symptoms had disappeared. She is now walking about and ready to go home.

The tumor, as you see, is of the solid variety with many areas of cystic degeneration and necrosis. On removal it measured about 30 cm. in diameter. It rested upon the transverse colon and was attached for several centimeters to the transverse mesocolon. The tumor surface between the mesocolon and the stomach is covered by a layer of omentum, so it is impossible to say whether the tumor arises from the mesocolon or from the omentum.

Since hardening the specimen it is readily seen that the tumor has no organic connection with the bowel.

A more minute pathological report will be made later, but on hurried microscopical examination the tumor seems to be sarcoma.

Gonorrhoeal Endocarditis, Exhibition of Specimens. Drs. Harris and Johnston.

(To be published later.)

SUMMARIES OR TITLES OF PAPERS BY MEMBERS OF THE HOSPITAL AND MEDICAL SCHOOL STAFF APPEARING ELSEWHERE THAN IN THE BULLETIN.

SAMUEL AMBERG, M. D. An Unusual Case of Spasmus Nutans.—*Archives of Pediatrics*, November, 1901.

CHARLES RUSSELL BARDEEN, M. D., and WARREN HARMON LEWIS, M. D. Development of the Limbs, Body-Wall and Back in Man.—*American Journal of Anatomy*, 1901, Vol. I, No. 1.

LEWELLYS F. BARKER, M. D. On the Clinical Aspects of Plague.—*American Journal of the Medical Sciences*, October, 1901.

JOSEPH C. BLOODGOOD, M. D. Blood Examinations as an Aid to Surgical Diagnosis.—*Medical News*, August 31, 1901; *Maryland Medical Journal*, September, 1901.

GEORGE BLUMER, M. D. The Bacteriology of Lobular Pneumonia, especially in adults. *Proceedings of the New York Pathological Society*, March, 1901; also in *Albany Medical Annals*, August, 1901.

——— The Bacteriology of Lobular Pneumonia, especially in Adults.—*Albany Medical Annals*, August, 1901.

——— The Present Status of the Infectious Theory of Malignant Neoplasms.—*The New York State Journal of Medicine*, November, 1901.

——— and ANDREW MACFARLAND, M. D. An Epidemic of Noma; Report of Sixteen Cases.—*American Journal of the Medical Sciences*, November, 1901.

WILLIAM D. BOOKER, M. D. The Early History of the Summer Diarrhœas of Infants.—*Archives of Pediatrics*, July, 1901.

THOMAS R. BROWN, M. D. On the Treatment of Tetanus, with Report of a Case that Recovered under Symptomatic Treatment Alone.—*Journal of the Alumni Association of the College of Physicians and Surgeons*, Baltimore, July, 1901.

——— The Diagnosis, Actiology, Prophylaxis, and Treatment of Cystitis, Pyelitis, and Pyelonephritis in Women.—*New York Medical Journal*, August 31, 1901.

——— The Practical Value of Blood Examination in Medicine and Surgery.—*American Medicine*, October 19, 1901.

H. WARREN BUCKLER, M. D. Care of the Indigent Tuberculous.—*Maryland Medical Journal*, August, 1901.

HARVEY CUSHING, M. D. Concerning the Poisonous Effect of Pure Sodium Chloride Solutions upon the Nerve-Muscle Preparation.—*American Journal of Physiology*, October 1, 1901.

——— Haller and His Native Town.—*American Medicine*, October 5 and 12, 1901.

JOSEPH ERLANGER, M. D. and ALBION WALTER HEWLETT, M. D. A Study of the Metabolism in Dogs with Shortened Small Intestines.—*The American Journal of Physiology*, September 1, 1901.

JOHN M. T. FINNEY, M. D. Anaesthetics in Heart Disease.—*American Journal of the Medical Sciences*, August, 1901.

——— and LOUIS P. HAMBURGER, M. D. The Relation of Appendicitis to Infectious Diseases.—*American Medicine*, December 14, 1901.

SIMON FLEXNER, M. D. A Comparative Study of Dysenteric Bacilli.—*Centralblatt für Bakteriologie Parasitenkunde und Infectionskrankheiten*, Bd. 30, No. 12.

——— The Pathology of Bubonic Plague.—*American Journal of the Medical Sciences*, October, 1901.

W. W. FORD, M. D. Classification of Intestinal Bacteria.—*Journal of Medical Research*, Vol. 1, No. 1.

THOMAS B. FUTCHER, M. D. Fusel-Oil Poisoning, with Special Reference to the Copper-Reducing Substances Eliminated in the Urine.—*American Medicine*, August 10, 1901.

——— Cirrhosis with Pigmentation.—*The Journal of the American Medical Association*, September 28, 1901.

NORMAN MCLEOD HARRIS, M. D. and WARFIELD T. LONGCOPE, M. D. Micrococcus Zymogenes: Some Additional Observations upon its Occurrence.—*Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten.* Erste Abt. Bd. 30, No. 9.

AUGUST HOCH, M. D. On Certain Studies with the Ergograph.—*The Journal of Nervous and Mental Disease*, November, 1901.

WILLIAM H. HOWELL, M. D. and C. E. BRUSH, JR. A Critical Note upon Clinical Methods of Measuring Blood Pressure.—*Boston Medical and Surgical Journal*, Aug. 8, 1901.

HENRY BARTON JACOBS, M. D. The Treatment of Consumption in Local Sanatoria.—*Maryland Medical Journal*, December, 1901.

WALTER JONES, M. D. and JOHN AUER. On the Oxidation of Native Pigments.—*The American Journal of Physiology*, 1901, Vol. V, No. 6.

HOWARD A. KELLY, M. D. Scratch-Marks on the Wax-tipped Catheter as a Means of Determining the Presence of Stone in the Kidney and in the Ureter.—*The American Journal of Obstetrics*, October, 1901.

IRVING PHILLIPS LYON, M. D. The Clinical Study of the Blood. A Brief Guide to the Application of Blood Examination to Medicine and Surgery. Reprinted from *Gaylord and Aschoff's Principles of Pathological Histology*, American Edition, 1901, being Chapter XVIII. Illustrated with one colored lithographic plate, one heliotype plate, and four wood-cuts.

This is one of the briefest (35 pages), yet most complete chapters on the principles and application of blood examina-

tion to clinical medicine and surgery, that has appeared in any general text-book. The first half of the paper is devoted, to a description of the various elements of the blood, the methods and technique of examination, and the general facts and principles of the physiology and pathology of the blood in health and disease. The second part of the paper treats of the special pathology of the blood and describes in the briefest form consistent with clearness the blood picture in nearly two hundred different morbid affections, arranged in alphabetical order, with special notes under each disease on differential diagnosis. References to the literature are given in footnotes.

——— Blood Examination Applied to Surgery. Reprinted from *Park's Surgery by American Authors.* Third Edition, 1901, being Chapter III.

A brief chapter (13 pages) written to supply the surgeon with practical data on the value of blood examination for diagnosis and prognosis in surgical affections. The general principles and facts of blood examination are first elucidated in a systematic manner and then the application of these principles to special morbid processes of surgical interest is described in a limited number of surgical affections.

——— and CHARLES CARY, M. D. Pseudomembranous Inflammation of the Mucous Membranes Caused by the Pneumococcus. Review of the Literature and Report of a Case of Pneumococcic Pseudomembranous Exudation on the Mucous Membranes of the Mouth, Tongue, Throat, Nose, Eyes, Glans Penis, Anus, etc., Complicating Acute Lobar Pneumonia.—*Transactions of the Association of American Physicians,* Vol. XVI, 1901; and *The American Journal of the Medical Sciences,* October, 1901.

Summary of case: Acute lobar pneumonia of both bases, with development during the first ten days of a profuse pseudomembranous exudate, first upon the tonsils and quickly extending to the mucous membranes of the lips, tongue, mouth, palate, throat, and nose and transferred to the eyes, glans penis, and anus; physical signs of fibrinous pleuritis; marked and persistent tympanites; membranous shreds and mucus in the stools. Microscopic examination: bacillus diphtheriæ, streptococcus, saccharomyces albicans, etc., absent; diplococcus pneumoniæ present in abundance in the sputum and in the exudate from all locations, grown in cultures and injected into a rabbit and recovered from the organs and blood after death. Diagnosis: pneumococcic infection resulting in acute pneumonia, pleurisy, and fibrinous exudation upon the mucous membranes.

The literature of pneumococcic pseudomembranous inflammation of the mucous membranes is reviewed and many cases cited, under the following divisions:

I. *Cases of Pseudomembranous Inflammation of Mucous Membranes Occurring in Association with Pneumonia.* This class includes (*a*) cases in which the pneumococcic origin of the croupous exudate upon the mucous membranes was not proved, but merely suggested by its association with pneumonia, and (*b*) cases in which the pneumococcus was shown by bacteriologic methods to be the specific agent in producing the lesion.

II. *Cases of Pseudomembranous Inflammation of Mucous Membranes of Pneumococcic Origin, Independent of Pneumonia.* The involvement of the various mucous membranes of the body in a pseudomembranous process caused by the local action of the pneumococcus is probably less infrequent than would be inferred from the almost total absence of mention of such a process in the text-books. The course of such cases is usually favorable.

——— Cancer Distribution and Statistics in Buffalo for the Period 1880-1899, with Reference to the Parasitic Theory.—*Third Annual Report of the New York State Pathological Laboratory of the University of Buffalo,* for the year 1900. Albany, N. Y., 1901.

The statistical method is adopted in this study, following up the suggestive findings of Behla at Luckau, in Germany. The main purpose was to find whether there occurred in the city of Buffalo any *local foci of the disease* in special regions of the city or in certain houses, out of proportion to the population of such places, and in case such foci occurred, what relation existed between them and their natural environments and the conditions of race, social status, and habits of the population. The statistics were collected from the original official certificates of death, signed in each case by a physician, preserved as the mortality records of the board of health of the city of Buffalo. All non-resident cases were excluded. The statistics embraced 2299 cases occurring during the twenty years, 1880-1899. The residence of each of these cases is indicated on a large (4 by 3 feet) street map of the city by colored dots. The results of the investigation are presented under the following headings: 1.) House Distribution as shown on the City Map. 2.) Multiple-case houses ("Cancer Houses"). 3.) Increasing Cancer Rate. 4.) Race Distribution. 5.) Age Distribution. 6.) Sex Distribution. 7.) Anatomical Distribution.

Some of the more important results of this study are briefly indicated in the following summary:

(1) The house distribution of cancer on the map shows an area of marked concentration in the German wards. No other relation than that of race can be determined to exist between this area of concentration and local conditions.

(2) That there is a real relation between this local concentration and race (German) is further indicated by the race table, which shows that cancer is many times more frequent among the foreign-born and particularly the Germans than the native-born. The latter fact is also verified by the United States census for 28 large cities. The cancer rate of foreigners, in general, was 4.59 times the rate for the native-born and the corresponding rate for Germans (and Poles) was 4.81.

(3) The Germans (and Poles) were further specially distinguished from other classes by the high rate (43.8 per cent.) of involvement of the stomach, 2.08 times the rate (21 per cent.) shown by the native born. Cancer of the stomach, therefore, was ten times more frequent in the Germans (and Poles) than in the native-born in Buffalo, for equal numbers of each. Such high figures seem hard to explain on the embryonic or irritation theories and tend to support the parasite theory of cancer, by supposing that the peculiar diet of the Germans is more liable to contamination with a parasite of cancer than the more ordinary diet of other classes. Cancer of the uterus and breast in Germans (and Poles) was correspondingly low, being hardly more than half as frequent as in the native-born. This fact seems to be a further argument for the parasitic as opposed to the embryonic or irritation theories, considering the fact that the birth rate and the habit of nursing at the breast (conditions predisposing to degeneration of these organs) are greater among Germans than native-born women.

(4) The ratio of males to females, the latter taken as 100, was 93 for Germans (and Poles) and from 51 (native-born) to 61 (all Europeans except Germans and Poles) for all other races and classes. The high German male rate is probably directly dependent upon the high rate of cancer of the stomach (especially in males) and the low rate of cancer of the uterus

and breast (females) found to characterize the Germans as opposed to other races.

For all classes the ratio of males to females was found to have risen during the twenty years covered by the investigation. This rise was very slight for the native-born.

(5) An increase in the general cancer rate from 32 to 53 per 100,000 of population (65 per cent.) took place from 1880 to 1899. A similar increase has been shown in all countries. This increase is thought to be partly real and not entirely apparent. The rate of increase is shown to depend in part at least upon changes in the proportion of the foreign-born, as the cancer rate in the foreign-born is so much higher than in the native-born.

In conclusion the writer notes the sources of unavoidable error in the statistical method of investigation and advises caution in making deductions. Conclusions can be accepted only after repeated and thorough confirmation, and until then all generalizations should be avoided or treated merely as suggestive possibilities that may stimulate to further investigation.

W. G. MACCALLUM, M. D. A Case of Multiple Myeloma.—*The Journal of Experimental Medicine*, 1901. Vol. VI, No. 1.

—— and S. S. BUCKLEY, V. S. Acute Epizoötic Leucoencephalitis in Horses.—*The Journal of Experimental Medicine*, 1901. Vol. VI, No. 1.

JOHN N. MACKENZIE, M. D. The Study of Laryngology in the University and in the Higher Medical Education.—*Journal of the American Medical Association*, July 20, 1901.

EUGENE L. OPIE, M. D. Filarial Lymphatic Varix.—*American Journal of the Medical Sciences*, September, 1901.

WILLIAM OSLER, M. D. On the Advantages of a Trace of Albumin and a Few Tube Casts in the Urine of Certain Men Above Fifty Years of Age.—*New York Medical Journal*, November 23, 1901.

J. HALL PLEASANTS, M. D. Bacteriological Diagnosis of Typhoid Fever from a Clinical Standpoint.—*Journal of the Alumni Association of the College of Physicians and Surgeons*, Baltimore, July, 1901.

OTTO G. RAMSAY, M. D. A Case of Congenital Malformation of the Female Generative Organs.—*Yale Medical Journal*, December, 1901.

ROBERT L. RANDOLPH, M. D. Double Suppurative Irido-Choroiditis in Association with Purpura Hemorrhagica.—*Archives of Ophthalmology*, 1901, Vol. 30, No. 4.

—— Herpes Zoster Ophthalmicus Resulting in Loss of the Eye.—*Archives of Ophthalmology*, 1901, Vol. 30, No. 4.

HUNTER ROBB, M. D. The Advantages and Disadvantages of Drainage after Abdominal Operations.—*Annals of Gynecology and Pediatry*, September, 1901.

—— Two Cases of Brain Tumor in Gynecological Practice.—*The American Journal of Obstetrics*, October, 1901.

J. ERNEST STOKES, M. D. The Importance of an Early, Definite Diagnosis of Appendicitis.—*The Carolina Medical Journal*, June, 1901.

WILLIAM SYDNEY THAYER, M. D. Observations on the Frequency and Diagnosis of the Flint Murmur in Aortic Insufficiency.—*American Journal of the Medical Sciences*, November, 1901.

—— On the Occurrence of Strongyloides Intestinalis in the United States.—*The Journal of Experimental Medicine*, 1901, Vol. VI, No. 1.

SAMUEL THEOBALD, M. D. The Evolution of the Ophthalmoscope and what it has done for Medicine.—*Transactions of the Medical and Chirurgical Faculty of the State of Maryland*, April, 1901.

Abstract of an address delivered before the Medical and Chirurgical Faculty of Maryland at the opening of its one hundred and third annual session, and published in full in the New York Medical Journal for June 22, 1901.

The selection of the theme was suggested by the fact that the year 1901 is the fiftieth anniversary of the invention of the ophthalmoscope by Helmholtz. By way of introduction, a brief resumé is given of the investigations regarding the luminosity of the eyes of certain animals, and of the human eye under certain conditions, by Prévost, Rudolphi and Behr and, at a later period, by Cumming and Brücke, of which Helmholtz's invention seemed but the logical outcome. Of these investigators Cumming was the only one who had in view the discovery of a method of detecting pathological changes in the interior of the eye.

The contrivance of an ophthalmoscope, by scraping off a little of the silvering from the back of a plain mirror which was set obliquely in a suitable tube, by Charles Babbage, F. R. S., in 1847, four years before Helmholtz's invention, "was an event of much interest in the history of ophthalmoscopy, though it had no bearing upon Helmholtz's invention and exerted absolutely no influence upon the subsequent evolution of the ophthalmoscope." Through the failure of Wharton Jones, to whom Babbage submitted his invention, to appreciate its value, it attracted no attention, and, in fact, was wholly lost sight of until after Helmholtz described his instrument; nevertheless, the credit of being the inventor of the first ophthalmoscope is undoubtedly due to Babbage. It is a remarkable fact that in not one of the numerous biographical sketches of Charles Babbage, who was most widely known through his efforts to construct a calculating machine, and who, in his later years, gained great notoriety because of his "fierce hostility" to organ-grinders, is there the slightest reference to his having invented an ophthalmoscope.

Helmholtz's ophthalmoscope was unquestionably the legitimate parent of all later ophthalmoscopes; it was also the first instrument with which the background of the living eye was seen *distinctly*. Furthermore, Helmholtz was absolutely the first to suggest the *indirect* method of ophthalmoscopy (though the credit for this is commonly given to Ruete); and it was he who directed the world's attention to the subject. Still, what was essential in his ophthalmoscope—the plain glass reflector—was not wholly original, having been but the practical application of von Erlach's observation that the light reflected from his spectacle lenses at times caused the pupils of persons in front of him to emit an unusual glow; and what was original—the insertion of a concave lens between the reflector and the eye of the observer—was "distinctly not essential" and was moreover, "the outcome of a misconception—a fortunate misconception, as it turned out—upon his part."

The employment of this concave "ocular," was the result of Helmholtz's belief that the eye under examination would tend

to focus for the image of the nearby flame, and hence that the light reflected from its fundus would leave the cornea in converging rays, which must needs be rendered parallel or divergent in order to afford clear vision to the observing eye. As a matter of fact, the observed eye shows but little inclination to employ its focussing power, especially in the direct method of examination which Helmholtz chiefly relied upon. On the other hand, in this method particularly, the beginner in the use of the ophthalmoscope finds it very difficult to relax *his* accommodation or to focus for other than divergent rays of light, and is, therefore, greatly helped by employing a concave lens. Thus it came about that the concave lens used by Helmholtz, though it was not an essential feature of a successful ophthalmoscope, and was employed by him to meet an unreal difficulty, was, nevertheless, of the greatest assistance to him and his earlier pupils, who were, of course, all neophytes in ophthalmoscopy.

Within a few months after Helmholtz announced his invention, Epkens, an instrument-maker of Amsterdam, constructed an ophthalmoscope in which a plane mirror, with the silvering removed from a small space in its center, was substituted for the less efficient glass plates used by Helmholtz, this being essentially a return to the earlier instrument of Babbage. A still more decided advance was made by Professor Ruete, of Göttingen, who, in 1852, suggested the employment of a *concave* mirror in place of the plane mirror of Epkens, and thus made indirect ophthalmoscopy, the value of which he was the first to appreciate, practicable. It is worthy of remark that, although the subsequent evolution of the ophthalmoscope was almost wholly the work of ophthalmologists, they took no part in the scientific observations which led to its invention, and had no hand in the invention itself or in the improvements made in it up to the time of Ruete.

The adaptation of the ophthalmoscope to accurate optometry to the measurement of the refraction of the eye, constitutes the next decided step in its evolution, and here American ophthalmologists come definitely to the fore, the largest measure of credit being due to the late Dr. Edward G. Loring, of New York, for bringing the refracting ophthalmoscope to its present state of perfection. The ophthalmoscope of Mr. Morton, of London, is, perhaps, the strongest rival of the perfected instrument of Loring, with its tilting mirror, revolving quadrant, etc., but is hardly its equal, though it has undoubted merits.

As usually happens under such circumstances, when the ophthalmoscope was first brought to the world's attention by Helmholtz, much skepticism was shown as to its real value, and it was contended that its employment, even for a few moments, would be "highly injurious," and that the knowledge gained from it would be more than offset by the harm it was likely to do. However, in spite of such pessimistic prognostications, it grew in favor rapidly, and soon came to be appreciated at its true worth. Among the first to recognize its value and acquire skill in its use were Von Graefe and Liebreich, in Germany; Donders, in Holland; Jaeger, in Austria; Desmarres and Sichel, in France; Bowman and Hulke, in England, and E. Williams, of Cincinnati, in this country. These names one is not surprised to find connected with the early history of ophthalmoscopy; but one hardly expects to be told, as Clifford Allbutt tells us in the introduction to his work on *The Ophthalmoscope*, that Mr. Spencer Wells was among the first in England (in an article in the Medical Times for September 10, 1853) to insist upon the great value of the ophthalmoscope in diseases of the eye; or to learn, from a comprehensive and interesting account of the earlier ophthalmoscope by the late Dr. Christopher Johnston, published in The Transactions of the Medical and Chirurgical Faculty of Maryland, in 1854, that Dr. George W. Miltenberger, whose name we associate with a very different branch of medicine, had already, at that early period, acquired proficiency in the use of the ophthalmoscope.

To comprehend the veritable revolution which the invention of the ophthalmoscope brought about in ophthalmology, one needs but to glance over the table of contents of any of the standard works upon diseases of the eye published prior to this period, and note the varieties and sub-varieties of "amaurosis" which are enumerated, the causes assigned for it and the remedial measures suggested to combat it. Ophthalmology deprived to-day of the ophthalmoscope might be likened to a rudderless ship; but a ship bereft, at once, of compass and sextant and rudder as well, would seem to afford a still more apt comparison.

But ophthalmology is not the only department of medicine that is beholden to the ophthalmoscope. The specialists in diseases of the eye had hardly earned its value before his brethren interested in affections of the brain and nervous system began to realize how great a boon it was to them as well. Hughlings Jackson, in London, and Clifford Allbutt, in Leeds, were the first to approach the subject from the standpoint of the neurologist, and they may well be called the fathers of medical ophthalmoscopy. Their labors have been well supplemented by another English worker in this same field, Dr. W. R. Gowers. Besides affections of the brain and nervous system there are many other maladies, such as Bright's disease, diabetes, pernicious anæmia, leucocythæmia, angio-sclerosis, etc., in which intraocular changes, more or less characteristic and hence of diagnostic value, are revealed by the ophthalmoscope.

WILLIAM HENRY WELCH, M. D. The Relation of Yale to Medicine.—*Yale Medical Journal*, November, 1901.

J. WHITRIDGE WILLIAMS, M. D. Pelvic Indications for the Performance of Cesarean Section.—*American Medicine*, September 28, 1901.

HUGH H. YOUNG, M. D. Chronic Cystitis Due to Bacillus Typhosus—Report of a Case of Seven Years' Duration. —*Maryland Medical Journal*, November, 1901.

——— Genital Tuberculosis, with Special Reference to the Seminal Vesicles.—*Annals of Surgery*, November, 1901.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read, and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly.

Volume XII is now completed. The subscription price is $1.00 per year. The set of twelve volumes will be sold for $23.00.

NOTES ON NEW BOOKS.

Operative and Practical Surgery for the Use of Students and Practitioners. By THOMAS CARWARDINE, M. S (Lond.), F. R. C. S., Assistant Surgeon Bristol Royal Infirmary, with 550 illustrations most of which are original drawings by the author. (*Bristol: John Wright & Co., 1901.*)

This manual of 661 pages is intended to give students and practitioners the essentials of operative and practical surgery, as the writer tells us in his preface. A careful examination of the book seems to indicate that he has accomplished his purpose very well. While in so small a compass only a very concise and often incomplete discussion of the subjects under consideration can be given, the book on the whole is quite satisfactory. There are, however, numerous points which might be improved upon specially for the use of American students. In the present stage of medical education when every student is supposed to own a special book on gynaecology and on diseases of the eye and ear it seems out of place to introduce a discussion of these subjects when the space might be better taken up with a more complete discussion of general surgical topics. In a text-book the consideration of methods of extracting teeth also seems out of place as such work is almost universally turned over to dentists in this country at least. In the general considerations on technique we find antiseptic treatment advocated practically to the exclusion of aseptic technique, quite contrary to the general views of most American surgeons. We regret to find that the writer believes that the use of gloves is unnecessary and cumbersome. In the treatment of fractures numerous splints are depicted and are advised for the ordinary fractures of the leg, while the more simple and effectual method by use of plaster of Paris casts, is not even mentioned. In the chapter on brain surgery, the technique of trephining is described, but the osteoplastic flap which is now generally considered the best method of opening the skull is not even mentioned. In the chapter on the surgery of the chest, a description is given of the method of opening the pleural cavity for empyema without the removal of a rib, a method which we believe to be unsafe and unsurgical. In discussing the treatment of hydrocele the various methods of tapping with injection, excision of a part of the sac and drainage, and complete excision are all described without any statement as to the comparative merits of the various procedures or their adaptability to individual cases. We notice the same fault in connection with many other operations. While these and some other points might be criticized, in many other respects the book is most excellent. The illustrations are as a rule, simple and very good. Most modern surgical procedures are at least mentioned and usually the best methods are adequately described. On the whole the text-book is as satisfactory as most of those which come into the hands of students, although as we have suggested, some changes would be desirable to adapt the book to use in American medical schools.

A Text-Book of the Practice of Medicine. By JAMES M. ANDERS, M. D. Fifth edition. (*Philadelphia and London: W. B. Saunders & Co., 1901.*)

As the previous edition of this text-book was carefully reviewed about a year ago, there is little additional to say regarding this one. Dr. Anders has made changes wherever the research work of the past year has rendered them necessary and he is to be complimented on the general thoroughness with which changes and additions have been made.

A Manual of Determinative Bacteriology. By FREDERICK D. CHESTER, Bacteriologist of the Delaware College Agricultural Experiment Station, etc., etc. (*New York: The MacMillan Co., 1901.*)

With the aim to facilitate identification of bacteria and to bring before the minds of workers in bacteriology the principles underlying scientific nomenclature, the author has performed a worthy service in his excellently compiled book.

The title well indicates the chief scope and object of the work, and he who carefully reads through the pages will, even though he take issue with the author now and then, find sufficient to highly praise.

Chapter I deals with the general morphology of bacteria in a clear, concise manner.

In Chapter II, the author gives a good resumé of cultural and biochemical characters, and draws attention to the present day fashion of descriptive verbosity, successfully demonstrating what a few well-chosen words can do in clearly and concisely describing all conditions as they are found. Here might be mentioned, a little out of place, possibly the existence of a glossary of terms at the end of the book which will be found of great assistance in attempting description of a species.

In discussing the preparation of media the author follows the scheme, as laid down for such, by the Bacteriological Committee of the American Public Health Association, a point not as yet sufficiently emphasized by American authors.

Chapter III. This is the writer's *pièce de résistance*. The opening pages treat of the relation of bacteria to other organic forms of life; the classification of them into families; the laws of nomenclature; and, to facilitate study, the arrangement of the species into groups.

In the main, the classification and definitive terms of Migula have been followed, although, in dealing with the tubercle bacillus and other branching forms the writer favors those of Lehrmann and Neumann.

Much time and labor have evidently been expended upon the grouping of the species, and the result as a whole is satisfactory, but it is difficult to understand the reasons for placing B. zenkeri and B. zopfii in the group of bacteria forming endospores, and why such organisms as Bact. bordonii, Bact. crassum and Bact. rhinoscleromatis have been removed from the Friedländer group.

Typographical errors of omission and commission are occasionally to be noted, such as "spirilli" for "spirilla" (p. 41, sixteenth line from the top), and "rhinosclermatis" for "rhinoscleromatis" (throughout the book), otherwise the typography is pleasing to the eye. A few illustrations are to be found which facilitate the explanations in the text.

The book should be given a cordial reception because it is helpful. And Mr. Chester is deserving of the thanks of the many bacteriologists in this country, for the time, energy and thought expended in rendering clearer much that has been heretofore obscure, and in pointing out the way to a more truly scientific comprehension of facts and principles involved.

Nov. 30th 1901. N. MacL. H.

A System of Physiologic Therapeutics. A Practical Exposition of the Methods, other than Drug-Giving, Useful in the Prevention of Disease and in the Treatment of the Sick. Edited by SOLOMON SOLIS COHEN, A. M., M. D., Professor of Medicine and Therapeutics in the Philadelphia Polyclinic; Lecturer on Clinical Medicine at Jefferson Medical College; Physician to the Philadelphia Hospital, etc. Volume III—

Climatology, Health Resorts, Mineral Springs. By F. PARKES WEBER, M. A., M. D., F. R. C. P. (Lond.), Physician to the German Hospital, Dalston; Assistant Physician North London Hospital for Consumption, etc. With the Collaboration for America of GUY HINSDALE, A. M., M. D., Secretary of the American Climatological Association, etc. In two Books. Book I—Principles of Climatotherapy—Ocean Voyages—Mediterranean, European and British Health Resorts. Book II—Mineral Springs, Therapeutics, etc. Illustrated with Maps. Price for the complete set, $22.00 net.

These two volumes devoted to the general subject of climatology consist in the aggregate of 700 pages, barring indices. The first 70 pages deal with climate, the air, absolute and relative humidity, barometric pressure and the like. Then in a few pages is discussed the physiological effects of low and high altitude, warm and cold, dry and moist climates. One can but notice a slight degree of scepticism in accepting the mosquito theory of the propagation of malaria, on p. 48: "Malaria, which a generation back was prevalent in certain parts of England has been banished by the drainage of fens and marshes. The prevalent tendency is to explain this by the abolition of favorable breeding places for mosquitoes, in particular those of *Anopheles*, which have been demonstrated to be the intermediate hosts of the plasmodia of malaria. The exclusive rôle of the mosquito as a carrier of malarial infection has not, however, been proved and there may be other factors not yet demonstrated."

Part II covering 487 pages is given up to a description of the health resorts of the whole world. Each country is considered and few towns or cities escape. One naturally turns to see what is said of places with which one is familiar and is disappointed to find how much like those of the ordinary guide books the descriptions are. For instance, "Royat (1480 feet) beautifully situated at the entrance of the Tiretaine Valley is 1¼ miles to the west of Clermont-Ferrand with which it is connected by train and electric tramway. The view from Royat over the fertile plain of the Limague toward the Forez Hills on the east is magnificent. The thermal muriated alkaline springs on whose account Royat has sometimes been called the "French Ems," have a great reputation in chronic gout, rheumatoid arthritis, chronic catarrhal conditions of the respiratory organs, etc. The springs of Royat contain more or less iron, bicarbonate as well as sodium chloride and sodium bicarbonate. Royat is a fashionable spa very much frequented during the season, especially from the middle of June to the middle of August, and the hotel accommodation is first-class."

Turning to the resorts of the United States the book falls open to Long Island, Volume IV, page 100. "Long Island lies south of Connecticut between 72° and 74° west longitude and 41° north latitude. At its western extremity lies a portion of the city of New York—the boroughs of Brooklyn and Queens—separated from Manhattan by the East River and containing over 1,250,000 inhabitants. At the time of its consolidation with New York city, Brooklyn was the fourth city of the United States in population. It is connected with Manhattan by a bridge over which a very large number of Brooklyn residents cross daily to and from their occupation. Other bridges are under construction. At the eastern end of Long Island 120 miles distant, is Montauk Point, used in 1898 as a camp for United States troops at the close of the Spanish-American war. Experience showed, however, that it was not well suited for that purpose. . . . The resorts of Long Island are quickly reached from New York city by rail and the nearer ones by water route and by trolley cars. Some are used principally as summer resorts and others as places of permanent residence, though these also have a great influx of visitors in the summer. The most accessible resort is Coney Island including Brighton Beach and Manhattan Beach. These are chiefly patronized for a few hours of holiday excursions in the afternoon and evening and provide for thousands of visitors of a somewhat 'mixed' character, a varied entertainment. Next in order on the south shore are the Rockaways, Long Beach, Babylon, Islip, Patchogue, Quogue, the Moriches, Chinnecock Hills, Southampton and Easthampton. Along the sound are Flushing, Little Neck, etc., etc. The chief attractions of all these resorts are the facilities they offer for bathing, boating and fishing. The climate is especially suitable for the neuraesthenic and for general relaxation from business cares."

These two descriptions taken at random, will give a fairly adequate idea of the character of the descriptions of the resorts mentioned. One chapter written by Dr. Titus Munson Coan of New York, is devoted wholly to the Hawaiian Islands. Careful and complete consideration is given to the climate, the winds, the rainfall and temperature of these islands.

For the physician the last part of the second volume devoted to the therapeutic effects of climate is the most valuable portion of the work. Here one finds the subject considered from the standpoint of general and particular diseases. For instance, the kind of climate, altitude etc., useful in gout and gouty conditions. Definite suggestions of value are given, though the tendency is still to such prolixity as to be of little avail to a physician or patient seeking a proper resort. For example, page 285, "The best American resorts for the treatment of gout and allied affections are Hot Springs, North Carolina, Las Vegas Hot Springs, New Mexico, Klamath Hot Springs, California and Mudlavia near Attica, Indiana. At Las Vegas, Klamath and Mudlavia mud baths are employed with great success. Other mineral springs worthy of mention are those at Bedford, Pennsylvania, Ukiah and Santa Ysabl, California, the Poland in Maine, Richfield, New York, the vichy spring at Saratoga, New York, and Buffalo lithia springs, Virginia. There are many other waters of value in the treatment of gout, some such as those of Glen Summit and Minnequa in Pennsylvania, depending like the Poland water on great purity and freedom in use. Others, such as Londonderry lithia, Buffalo lithia, Farmville lithia, depending in part on the contained salts of which lithium compounds are the least important."

In writing any book upon climatology and health resorts the author is necessarily somewhat embarrassed lest he display unwarrantable partiality in his description of single places. Yet in order that a book may be of maximum usefulness definite strong statements are needed. In a notice of volume I of this series in the BULLETIN the following words were used: "It is greatly to be hoped that the completed work will not become so voluminous as to lose its general usefulness." "The appearance of such a system of medicine is timely, as no author or authors have until now gathered together in one volume or series of volumes in English these methods which are so very important in the treatment of disease." To all who have strong feelings that often much more can be accomplished by so-called physiologic therapeutics than by the mere administration of drugs, much was hoped for in this system of Dr. Cohen's. That these volumes which have appeared are of value there can be no doubt, but that they are fulfilling all that was looked for is not true; probably our expectations were too high, perhaps unreasonable but the fear is irresistible that they are becoming too voluminous and diffuse, and that they will be found in medical libraries rather than upon the tables of the every-day practitioner, where they ought to be in order to do their greatest good in bringing about the reform so much needed in our treatment of disease, when every measure likely

to aid nature in the least shall be considered, and our thoughts shall no longer be so completely centred upon the Pharmacopœia.

A Treatise on the Acute Infectious Exanthemata including Variola, Rubeola, Scarlatina, Rabella, Varicella, and Vaccinia, with especial reference to diagnosis and treatment. By WILLIAM THOMAS CORLETT, M. D., L. R. C. P., Lond., Professor of Dermatology and Syphilology in Western Reserve University, etc., octavo, 592 pages. Illustrated by 12 colored plates, 28 half-tone plates from life and 2 engravings. (*Philadelphia: F. A. Davis Company, Publishers*, 1901.)

The necessary isolation of patients suffering from any one of the exanthemata and the risk of conveying the infection to a third person, render it impossible for the student to have free access to individuals suffering from the various infectious diseases. The vast majority of students are consequently graduated with the most inadequate practical knowledge of the various exanthemata. It was the recognition of this deplorable fact that prompted the author to publish the present volume. The author's excellent lantern-slide reproductions of photographs of the various exanthems are well known to many. The numerous excellent plates from photographs of actual cases, many with the characteristic tints accurately portrayed, undoubtedly add very materially to the value of the volume, and give one a splendid idea of the actual tints of the skin observed in the various diseases.

The description of the various diseases is preceded by an interesting historical sketch of the exanthemata, and it is worthy of note that the most dreaded of them still—small-pox was the first of which we have definite records.

The section on Variola is very full and the description with the plates should practically enable one who has never seen small-pox to recognize the disease. The section on Scarlatina written by Dr. E. P. Carter is in many respects the best in the book.

The volume fills a needed want and every student and practitioner will find it a useful book for purposes of reference.

Dorland's American Illustrated Dictionary. The American Illustrated Medical Dictionary. For Practitioners and Students. A Complete Dictionary of the Terms used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, and the kindred branches, including much collateral information of an encyclopedic character, together with new and elaborate tables of Arteries, Muscles, Nerves, Veins, etc.; of Bacilli, Bacteria, Micrococci, Streptococci; Eponymic Tables of Diseases, Operations, Signs and Symptoms, Stains, Tests, Methods of Treatment, etc., etc. By W. A. NEWMAN DORLAND, A. M., M. D., editor of the "American Pocket Medical Dictionary." Second edition, revised. Large octavo, nearly 800 pages, bound in full flexible leather. (*Philadelphia and London: W. B. Saunders & Company, 1901.*) Price, $4.50 net.

A notice of this convenient book of reference appeared in a recent number of the BULLETIN. There is little to be added in regard to the present edition as the changes which have been made are simply those which did not involve any disturbance of the pagination of the first edition. About one hundred new terms and definitions have been added without the sacrifice of any important words, in the former edition. To those physicians who desire a handy volume to lie upon the desk for ready consultation, this book may be commended as probably the most handy one in print. It is to be regretted that works of reference of this character which in the growing state of medical science are subject to constant change, are not printed by the linotype process, so that changes and additions can be freely incorporated in every edition. When the books are printed from stereotype plates, the necessity of fitting the new word into a specified pre-arranged space often renders the definitions unsatisfactory and the information which is given of a meagre ten-word-telegram character. This edition is clearly printed on thin paper and attractively bound in flexible leather.

Diseases of the Intestines. Their Special Pathology, Diagnosis and Treatment, with Sections on Anatomy and Physiology, Microscopic and Chemic Examination of the Intestinal Contents, Secretions, Feces, Urine, Intestinal Bacteria and Parasites; Surgery of the Intestines; Dietetics; Diseases of the Rectum. By JOHN C. HEMMETER, M. D., Philos. D., Professor in the Medical Department of the University of Maryland. In two volumes. Vol. I. Octavo: 742 pages. (*Philadelphia: P. Blakiston's Son & Co., 1012 Walnut Street, 1901.*)

In first taking up this volume one is at once impressed with the apparent magnitude of the work. When realizing, however, that it is only the first of two volumes, the second to appear later, one is almost overwhelmed. The work cannot be considered a students' text-book, for, with the demands now made on medical students, there is rather too much chaff to be searched in order to get at the wheat. We observe a verboseness of style which has not been absent from the author's previous publications. In justice to the author, however, the treatise is rather intended for the practitioner, for he says, "My own efforts, in this present publication, have been directed to furnishing the practitioner with a complete work, from which he may readily instruct himself concerning the most approved and modern methods of diagnosis and treatment of intestinal diseases."

The present volume is largely the work of the author, although it is in part a collaboration. The section on the "Anatomy and Histology of the Intestines" is written by J. Holmes Smith, M. D., of the University of Maryland; that on "Intestinal Bacteria" by Wm. Royal Stokes, M. D., and that on "The examination of Faeces and Urine" by Harry Adler, M. D., both of the same institution. The section on "Diseases of the Rectum" is by Thomas Charles Martin, M. D., of the Cleveland College of Physicians and Surgeons. The scope of the present volume is given in the title above. We prefer to reserve a fuller review and criticism of the work until after the appearance of the second volume, when fuller justice to the author can be done. The publishers have produced a most creditable volume. The paper and type are unusually good and the numerous reproductions excellent.

A Manual of the Practice of Medicine. By GEORGE ROE LOCKWOOD, M. D., New York. (*Philadelphia and London: W. B. Saunders & Co., 1901.*)

This work is smaller in size than the average text-book of medicine. The author in his preface says, "It is hoped that the work will meet the requirements of those who heretofore have been obliged to resort to the larger works of reference with which medical literature is so well supplied." This does not give a very clear idea as to the purpose of the book unless it be meant to take the place of the usual text-books. As we have said before, there should be no place for works designed to replace the standard text-books of medicine. It is probably possible to put the essential points of a text-book article in smaller space but any gain from doing so is doubtful. The authors of standard text-books, in all probability have already put the matter in as small a space as is consistent with their highest utility. Dr. Lockwood has in this work generally used his pages to good advantage but we may be pardoned for

doubting the necessity of his doing it at all. There are some points in the article on typhoid fever to which attention might be drawn, as an example of the evil of too much condensation. There is no mention of the frequent occurrence of typhoid bacilli in the urine apart from abscess of the kidney or pyelitis. In discussing relapses it is said that the interval between the original attack and the relapse "may extend to twenty-five days." This conveys the impression that this interval is the maximum, whereas it may be much longer. Then to say that "leucocytosis in typhoid fever is not marked" hardly gives a correct idea as to the usual diminished number of leucocytes in ordinary cases. Under the head of treatment, among other foods which *are to be avoided if possible* is included white of egg with water. If there is one form of diet which is useful above all others in typhoid fever, it is egg-albumen. We are quite in accord with the advice to avoid beef-peptonoids and beef-tea. That the main object of the Brand treatment is to reduce the fever, as is rather suggested, will hardly be supported by those who use it most. Its influence on other symptoms is of certainly equal importance. We would also take issue with the author in regard to his treatment of perforation, namely, "by warmth to the body and free stimulation, while opium should be given in full doses." In a robust person or during convalescence it is advised that operation "should be considered." Surely he who so advises has read but imperfectly the recent results of operation even in the most desperate cases. There is only one treatment for perforation and that is surgical, unless of course the patient be moribund when the diagnosis is made.

It must not be supposed that we take issue with the author as frequently in every article as in the one on typhoid fever, but we have given enough to show why we can not recommend his book without reserve.

Mt. Sinai Hospital Reports. Volume II, for 1899 and 1900. Edited for the Medical Board. By PAUL F. MUNDE, M. D., 1901.

This is a volume of 540 pages which contains the statistical reports of the various services and notes of many of the more interesting cases. The statistics are conveniently tabulated for reference. Among the medical reports is the account of an interesting series of six cases of diphtheria coexisting with typhoid fever, contributed by Dr. Manges. There are two articles by Drs. Bull and Libman on a case of Systemic Pyocyaneus Infection and on Interstitial Nephritis and Arteritis in the young. The surgical reports give the clinical notes of many cases and statistics of the results with added explanations as to the general rules of treatment and methods of operation. A valuable feature is the report of the anaesthesias. We notice that there is a marked preference for the use of chloroform. Several papers on various subjects in gynaecology, eye and ear work, etc., conclude the book.

An Introduction to Physiology. By WILLIAM TOWNSEND PORTER, M. D., Assoc. Prof. of Physiology in the Harvard Med. School. (*Cambridge: The University Press, 1901.*)

This book differs from most laboratory manuals in that the description of apparatus and methods of experimenting is accompanied by a certain amount of text in which the theoretical side of the experiments is dwelt upon to some extent. It seems therefore to be more complete than the usual laboratory books, for the ground that it covers, and is particularly well adapted to the use of earnest students capable of self-instruction. The preparation of the book shows great care, and the various forms of simple apparatus that have been designed to take the place of the more complicated instruments known to the laboratory workers, are worthy of especial commendation for their simplicity and economy. Indeed there can be no doubt that Dr. Porter's efforts to create an outfit of inexpensive apparatus suitable for laboratory experiments, will prove ultimately of great benefit to the teaching of physiology in the colleges and medical schools of this country. In the larger institutions under the guidance of professional physiologists and with workshops of their own, it will doubtless always remain true that each teacher will prefer his own designs for the simple apparatus used in class work, but in the majority of medical schools and in many colleges, the teachers are not likely to have the proper facilities for the construction of such instruments, and the opportunity to purchase an outfit at a reasonable cost ought to remove all obstacles to the introduction of laboratory courses.

From the standpoint of general usefulness the book suffers from a defect that is inherent to a greater or less extent in all laboratory manuals, that is, it is planned especially for the author's own courses and will therefore be difficult to use as a students' guide in the courses of other teachers, unless, indeed, these latter are changed to conform to the plan followed in the book. On the other hand, as a teacher's manual or as an aid to the individual worker deprived of the assistance of a competent instructor, the book should be most helpful, as it contains many suggestive experimental methods capable of further amplification if the necessity arises.

So far as the book purports to give an outline of the ideal course for medical students, it is in the opinion of the reviewer, open to the serious objection of lacking in simplicity. Much is touched upon, for instance in the electrical phenomena of muscle and nerve, that cannot at present be accepted as fundamental and probably therefore will have no immediate nor ultimate value to the medical student, in fact, will be more likely to lead to mental confusion than to mental enlightenment. Exactness in method and in reasoning can be secured best by experiments where results are clear and where meaning can be interpreted with reasonable certainty. So far as medical students are concerned, experimental work in Physiology should be planned with some reference to its usefulness in their future work. To reach this desirable end no sacrifice need be made in accuracy or training, it is only necessary to exercise care in the selection of the subjects and methods employed.

W. H. H.

A Text-Book of Medicine for Students and Practitioners. By Dr. ADOLF STRÜMPELL, Professor and Director of the Medical Clinique at the University of Erlangen. Third American edition, translated by permission from the Thirteenth German Edition, by HERMAN F. VICKERY, A. B., M. D., and PHILIP COOMBS KNAPP, A. M., M. D., with Editorial Notes by FREDERICK C. SHATTUCK, A. M., M. D. Octavo, 1253 pages, with one hundred and eighty-five illustrations in the text, and one plate. (*New York: D. Appleton & Company, 1901.*)

This admirable text-book continues to retain its deserving popularity. For the student and active practitioner it is an excellent work. It contains probably more reading matter than any other one-volume text-book on medicine published in English. The pages are larger and the type rather smaller than in most medical books. The illustrations have always been a feature of this work and they undoubtedly enhance its value. No text-book is so good, however, as to be beyond criticism. Were it not for the fact that the translators and editor have made many valuable additions and comments, the room for criticism would have been even greater. It is really rather surprising that a number of important observations of comparatively recent date have escaped the author's attention, a few of which are also omitted by the translators.

In reviewing the book, the section on diseases of the nervous system is, as it always has been, undoubtedly the best. We know of no text-book in which this department of medical diseases is better treated. The chapters on cardiac, constitutional and renal diseases are excellent.

In the chapter on typhoid fever we fail to find any mention whatever of typhoid cholecystitis, a not unimportant complication of the disease. We fear that the author has not fully appreciated the beneficial results from early surgical interference of typhoid perforation. He says, "If perforation occurs the treatment is much the same (as in haemorrhage). Above all, opium must be used in still larger dose, but, unfortunately, as a rule, in vain. The surgical treatment of peritonitis has rather more of a future and more success, but experience of this is still scanty." The statement is far too conservative when one remembers that in the hands of some surgeons there have been recoveries in from 30 to 45 per cent of the cases operated on, while at the most without operation only 1 or 2 per cent recover. The chapter on dysentery seems decidedly incomplete without any reference to Shiga's bacillus (bacillus dysenteriae), especially as this organism is now regarded as almost a specific germ in one form of this disease. The translators have saved the article on malaria by a very brief reference to the relation of the mosquito to the transmission of the disease. It seems strange that plague should have been omitted in the German edition. The chapter on this disease has been added by one of the translators. The Germans have been extraordinarily slow in recognizing the importance of an eosinophilia in trichinosis, from a diagnostic standpoint. No mention of this association was made by the author, although there is a brief reference to it in the translation. The old terms typhlitis and perityphlitis are retained. No reference is made to the theory as to the etiology of scurvy which is now finding many adherents, namely, that the disease is due to toxic materials in the foods—some unknown organic poison the product of decomposition, and not to an absence of fresh vegetables or the salts of fruits and vegetable. The chapter on diabetes mellitus is very good. No reference is made to the hyaline degeneration of the islands of Langerhans found by Opie in the pancreas in a considerable number of cases of diabetes, an observation which seems destined to be of great importance in the pathology of diabetes. These are some of the sins of omission that have occurred to us. We make no hesitation in stating, however, that in our judgment the book has few equals and we doubt whether it has a superior in any language.

A Syllabus of New Remedies and Therapeutic Measures, with Chemistry, Physical Appearance and Therapeutic Application, United States Pharmacopeial Convention, 1900; American Medical Association; New York State Medical Association, United States Pharmacopeial Convention, 1900; American Chemical Society, p. 229. Price $1.00 net. (*Chicago: G. P. Engelhard & Co., 1901.*)

The purpose of this book, as stated in the preface, is to furnish the busy practitioner with an accurate, condensed review of the reports on the new remedies, especially on those which synthetic chemistry has added to the physician's armamentarium. The matter, however, has been too much condensed to make the book of very much value to any one wishing to make a serious, thorough trial of any of the drugs mentioned, but as a means of quickly ascertaining something of the nature and application of these remedies, the work is of some value to the student.

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